Antiretroviral Adherence and Treatment Outcomes Among Adult Ethiopian Patients

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by

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A thesis submitted in fulfilment of the requirements for the

degree of

Doctor of Philosophy

Division of Pharmacy, School of Medicine, Faculty of Health

University of Tasmania, Hobart

March 2016

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The research associated with this thesis abides by the international and Australian codes on human and animal experimentation, the guidelines by the Australian National Ethics and Institutional Biosafety Committees of the University. All research involving Ethiopian patients with HIV/AIDS and healthcare providers was conducted under the approval of the Bahir Dar University Ethics Committee and Tasmanian Human Research Ethics Committee: Approval numbers H0012722 and H0012845.

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27th March 2016

STATEMENT OF CO-AUTHORSHIP

Given that this thesis is presented as a sequences of papers, either published, in press or submitted, statement of co-authorship are provided for each chapter. Due to this thesis format some repetition is expected.

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PUBLICATIONS

All publications listed resulted from work described in this thesis.

Peer-reviewed Journal Publications

1. Woldesellassie M Bezabhe, Gregory M Peterson, Luke Bereznicki, Leanne Chalmers, Peter Gee. Adherence to antiretroviral drug therapy in adult patients who are HIV-positive in Northwest Ethiopia: a study protocol. BMJ Open. 2013; 3(10):e003559.

   Chapter 3: *Candidate was the primary author; who in conjunction with authors 2-5 contributed to the design of the study. The candidate drafted the manuscript. All authors provided input into the writing of the study protocol.*

2. Woldesellassie M Bezabhe, Luke R Bereznicki, Leanne Chalmers, Peter Gee, Gregory M Peterson.

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3. Woldesellassie M Bezabhe, Leanne Chalmers, Luke Bereznicki, Gregory M Peterson, Mekides A Bimirew, Desalew M Kassie. Barriers and facilitators of adherence to antiretroviral therapy and retention in care among adult HIV-positive patients: a qualitative study from Ethiopia. PLoS One. 2014; 9(5):e97353.

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4. Woldesellassie M Bezabhe, Luke R Bereznicki, Leanne Chalmers, Peter Gee, Desalew M Kassie, Mekides A Bimirew, Gregory M Peterson. Adverse drug reactions and clinical outcomes in patients initiated on antiretroviral therapy: A prospective cohort study from Ethiopia. Drug Safety. 2015 38 (7): 629-639.

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5. Woldesellassie M Bezabhe, Leanne Chalmers, Luke R Berezniki, Gregory M Peterson. Adherence to antiretroviral therapy and virologic failure: a meta-analysis. Medicine 2016; in press.

   Chapter 7: *Candidate was the primary author; who in conjunction with author 3 conceived and designed the study. The candidate drafted the manuscript. Authors 1-3 provided input into the writing of the research article.*

Letter to the Editor

1. Woldesellassie M Bezabhe, Luke R Bereznicki, Leanne Chalmers, Peter Gee, Desalew M Kassie, Mekides A Bimirew, Gregory M Peterson. Authors' reply to Cotton and Nicol's comment on "Adverse drug reactions and clinical outcomes in patients initiated on antiretroviral therapy: a prospective cohort study from Ethiopia". Drug Safety 2015.

Conference abstracts

1. Woldesellassie M Bezabhe, Gregory M Peterson, Luke R Bereznicki, Leanne Chalmers. Adherence with antiretroviral drug therpy in adult HIV-positive patients. University of Tasmania, Graduate Research Conference 2012. Hobart, Septemeber 6 to 7, 2012.
2. Woldesellassie M Bezabhe, Leanne Chalmers, Luke R Bereznicki, Gregory M Peterson, Mekides A Bimrew, Desalew M Kassie. Barriers to, and facilitors of adherence to antiretroviral drugs and retention in follow-up care among adult HIV-postive patients: A qualitative study in Ethiopia. National Medicine Symposium 2014. Brisbane, May 21 to 23, 2014.
3. Woldesellassie M Bezabhe, Leanne Chalmers, Luke R Bereznicki, Gregory M Peterson, Mekides A Bimrew, Desealew M Kassie. Barriers to and facilitators of adherence to antiretroviral therapy: qualitative study from Ethiopia. AIDS 2014. Melbourne, July 20 to 25, 2014.
4. Woldesellassie M Bezabhe, Leanne Chalmers, Luke R Bereznicki, Peter Gee, Gregory M Peterson. Antiretroviral adherence and treatment outcomes among adult Ethiopian patients. Annual Conference of the Australasian Pharmaceutical Science Association. Hobart, November 29 to December 2, 2015.

We the undersigned agree with the above stated “proportion of work undertaken” for each of the above published or under review peer-reviewed manuscripts contributing to this thesis:

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ACKNOWLEDGEMENTS

This project was supported by Pharmacy, School of Medicine, University of Tasmania. I am grateful to the University of Tasmania for awarding International Postgraduate Research Scholarship (IPRS) to undertake my study.

I would like to express my sincere gratitude to my supervisor Professor Gregory Peterson for providing me with the opportunity to work on an interesting project that I believe will improve antiretroviral treatment outcomes in resource-limited settings, for his knowledge, motivation, suggestions, and understanding. His supervision assisted me in all the time of research and writing of this thesis.

I convey my heartfelt gratitude to Dr. Luke Bereznicki for his encouragement, insightful comments, and patience. Special thanks to Dr. Leanne Chalmers for her critical remarks and suggestions throughout the design and development of my PhD thesis. I owe my gratitude to Peter Gee for developing a custom-built website and assisting me in handling and processing the data.

I would like to pass my gratitude onto Dr. Desalew Makonnen, Dr. Mekides Alemu, and Mr. Endalkachew Admassie for their participation in the design and development of the project. Without your contribution to resolving technical and administration issues, successful completion of the project would not have been possible.

I would like to thank Mr. Adane Minayehu, Mr. Zemene Demelash, Mr. Dawit Demelash, Mr. Zewdneh Shewamene, and Ms. Tsion Kesete, who worked as researchers on the project. Without your enthusiasm and commitment to the project, none of this would have been possible.

I would like to thank the nurses, case-managers, and adherence support workers in both hospitals for their assistance during the recruitment and follow-up, organising access to patients' medical records, sharing your office and participating in the qualitative study. I am grateful to all study participants for their participation.

I would like to thank all the Division of Pharmacy staff and PhD students for their encouragement and support over the course of my study and to all my friends who have helped me in countless ways over the past four years. We had unforgettable times together that I will value.

My wife, Dr. Mekides Alemu, and my son Daniel gave me a purpose for working harder and a sense of purpose. My parents, Ato Mequanint Bezabhe Tessema and Wizero Dasashe Getahun Alemie, have all the time been exceptionally helpful to my education in more ways than one.

ABBREVIATIONS

Acronym	Definition
ACTG	AIDS clinical trial group
ADR	adverse drug reaction
AIDS	acquired immunodeficiency syndrome
ALP	alkaline phosphatase
ART	antiretroviral therapy
AST	aspartate aminotransferase
AUDIT	alcohol use disorder identification test
BID	twice daily
BMI	body mass index
BMQ	belief about medicines questionnaire
BUN	blood urea nitrogen
CMA	comprehensive meta-Analysis
CCR	chemokine co-receptor
CD4	clusters of differentiation 4
CDC	Centers for Disease Control and Prevention
CES-D	Centre for Epidemiological Studies-Depression
CI	confidence interval
CNS	central nervous system
CYP	cytochrome P450

ABBREVIATIONS

Acronym	Definition
DAIDS AE	division of AIDS adverse events
DHHS	US Department of Health and Human Services
dsDNA	double-stranded deoxyribonucleic acid
DOT	directly observed therapy
EDM	electronic drug monitoring
EFV	efavirenz
ETB	Ethiopian birr
FDA	Food and Drug Administration
FG	focus group
gp	glycoprotein
Hb	haemoglobin
HBV	hepatitis B virus
HCR	healthcare relationship
HCV	Hepatitis C virus
HDI	Human Development Index
HLA	human leukocyte antigen
HIV	human immunodeficiency virus
HSI	HIV-symptom index
ICSR	individual case safety report

ABBREVIATIONS

Acronym	Definition
IN	integrase
INST	integrase strand transfer inhibitor
IQR	interquartile range
MEMS	medication event monitoring systems
MPR	medication possession ratio
NCD	necessity-concern differential
NGO	non-governmental organisation
NNRTI	non-nucleoside reverse transcriptase inhibitor
NRTI	nucleoside/nucleotide reverse transcriptase inhibitor
NVP	nevirapine
OI	opportunistic infection
OR	odds ratio
PI	protease inhibitor
PR	protease
PRISMA	preferred reporting items for systematic reviews and meta-analyses
RCT	randomised control trial
RevMan	review manager
rHuEPO	recombinant erythropoietin alpha

ABBREVIATIONS

Acronym	Definition
RNA	genomic ribonucleic acid
RT	reverse transcriptase
SD	standard deviation
SJS	Steven-Johnson syndrome
T20	enfuviritide
Tat	trans-activator-transcription
TDF	tenofovir
TEN	toxic epidermal necrolysis
UDP	uridine diphosphate
UGT1A1	UDP glucuronosyltransferase 1 family, polypeptide A1
VAS	visual analogue scale
WHO	World Health Organisation
WBC	white blood cell
ZDV	zidovudine
3TC	lamivudine

ABSTRACT

The scale-up of antiretroviral therapy (ART) services has been one of the best achievements witnessed in the health sector in Ethiopia over the past decade. A total of 339,043 adults had received treatment for Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) in Ethiopia as of 2014, and this number is expected to increase over the coming years. Achievement of optimal medication adherence is becoming the greatest challenge in the management of HIV/AIDS. Patients with suboptimal adherence are at high risk of progression to AIDS, emergence of resistant viral strains, limited future treatment options, and higher treatment costs.

Data on barriers to, and facilitators of, adherence in Ethiopian HIV-positive patients taking ART remains inconsistent and incomplete. The available cross-sectional studies are limited in that they have only assessed limited variables at a single point in time and qualitative studies have not yet explored factors associated with medication adherence at the individual level. While one prospective study has investigated adherence to ART in Ethiopia, it was only conducted for 3 months and also did not focus on treatment-naïve patients.

The objectives of the body of work contained in this thesis were to fill these gaps using a mixed-methods approach that include both prospective quantitative and qualitative studies to establish the levels of medication adherence and identify a wide range of factors that influence medication adherence. We also assessed the incidence of adverse drug reactions (ADRs) and associated risk factors in Ethiopian patients with HIV/AIDS initiated on ART.

The main study was conducted in two hospitals in Northwest Ethiopia: Gondar University and Felege-Hiwot Hospitals. It began with a prospective study in which 246 adult HIV-infected patients initiated on ART were followed from the time of initiation to 12 months of therapy. Patients had appointments every month for 6 months and every 3 months thereafter in ART clinics; research pharmacists collected data in line with patients' appointment schedules in the ART clinics.

In a subsequent study, semi-structured interviews were conducted with 24 patients, of whom 11 had been lost to follow-up and were non-persistent with ART. In addition, focus group discussions were performed with 15 ART nurses and 19 case managers. Questionnaires and interview guides were developed through a systematic procedure to ensure reliability, validity, and cultural appropriateness.

Of 172 who completed follow-up in the prospective study, 130 (75.6%) had ≥95% adherence at 12 months. In the multivariate analyses, a higher baseline body mass index (BMI) (Odds Ratio (OR), 1.2; 95% CI 1.0, 1.4) and use of reminder devices (OR, 9.1; 95% CI 2.0, 41.6) were positively associated with adherence, while a higher HIV symptom and ADR distress score was an independent negative predictor of adherence (OR, 0.90; 95% CI 0.9, 1.0). Clusters of differentiated 4 (CD4) count increase was significantly higher in the adherent patients compared to non-adherent patients at 12 months (159 cells/μL [interquartile range (IQR), 72-324 cells/μL] vs. 132 cells/μL [IQR, 43-190 cells/μL]; p = 0.026). Patients who experienced a severe ADR were less likely (OR, 0.4, 95% CI 0.2, 0.9) to be adherent to ART. Logistic regression analysis indicated that taking zidovudine-

containing regimens (OR, 4.2, 95% CI 2.1, 8.4) or being unemployed (OR, 2.2, 95% CI 1.1, 4.3) were independent predictors of experiencing severe ADRs.

All factors that were independent predictors of adherence in our prospective study also emerged directly or indirectly as important factors influencing adherence in the qualitative study. The qualitative study identified economic constraints, perceived stigma and discrimination, fasting, religious belief, medication side effects, and dissatisfaction with healthcare services were major reasons for patients being non-adherent and lost to follow-up. Disclosure of HIV status, social support, use of reminder aids, responsibility for raising children, improved health on ART, and receiving education and counseling emerged as facilitators of adherence to ART.

In conclusion, this work rigorously evaluated barriers to, and facilitators of, adherence to ART in Ethiopian HIV-positive patients using a mixed-methods approach. It identified economic constraints such as food insecurity and severe ADRs as important barriers to adherence while use of reminder devices promote adherence. Implementation of measures to consistently monitor severe ADRs and economic constraints, and to promote use of reminder devices have the potential to improve adherence and treatment outcomes in HIV-positive patients taking ART.

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CHAPTER ONE

1. INTRODUCTION

1.1. HIV/AIDS

Since Human Immunodeficiency Virus (HIV)/Acquired Immunodeficiency Syndrome (AIDS) was detected in the United States in 1981, it has become one of the most dreaded scourges faced by humankind in the 21st century [1]. HIV destroys clusters of differentiation 4 (CD4)+ T cells that result in a decline in immune function [2]. Clinical stages of HIV progress from stage 1 (asymptomatic) to stage 4 (AIDS) [3]. AIDS-defining opportunistic diseases that decrease survival in patients with HIV infection include *Pneumocystis jiroveci* pneumonia, *Mycobacterium avium complex* disease, *Cytomegalovirus* disease, *Candida* oesophagitis, Kaposi's sarcoma, and lymphoma [4].

Around 36.9 million people were living with HIV/AIDS worldwide by the end of 2014. The majority of these people (25.8 million) live in sub-Saharan Africa [5]. New HIV infections have fallen by 35% worldwide since 2000. Of the total 2 million new HIV infections worldwide in 2014, 1.4 million were in sub-Saharan Africa [5]. Despite a reduction in new infections, the number of people living with HIV/AIDS is growing as the result of the combined effect of new HIV infections and, more importantly, significant expansion of access to antiretroviral therapy (ART), which has helped to reduce AIDS-associated deaths [5].

The rollout of ART in sub-Saharan Africa over the past 15 years is one of the world's largest public health interventions. At the end of 2002, about 52,000 people were on ART in sub-Saharan Africa. Currently, of the total 15 million people accessing ART worldwide as of March 2015, 10.7 million persons were from sub-Saharan Africa [5].

1.2. HIV-1 life cycle and antiretroviral targets

Sexual or parenteral contact with HIV-containing body fluids is a means to transmit HIV [6]. The routes of HIV transmission are different in different regions of the world [7]. Heterosexual transmission is the dominant mode of HIV transmission in sub-Saharan Africa and overall around the globe [2]. In the USA, Europe and Asia, one-third of HIV infection is due to the use of contaminated injection equipment [2].

Once infection occurs, the HIV-1 virus introduces its genetic material to host cells by direct fusion of the viral and host membranes [8]. HIV primarily infects CD4+ T cells, macrophages, and monocytes. The envelope glycoproteins of the viral-cell membrane, glycoprotein 120 (gp120) and glycoprotein 41 (gp41), are derived from a larger 160-kilo dalton precursor glycoprotein (gp160) [9]. Three gp120 surface glycoproteins attach through non-covalent binding with three gp41 transmembrane glycoproteins to form viral spikes [10, 11] which are necessary to mediate viral particle attachment and fusion to target cells [12]. The surface glycoprotein, gp120, triggers viral fusion by interacting with CD4 receptors and G-protein coupled transmembrane chemokine co-receptors (CCR5 and CXCR4) [13]. Drugs designed as fusion inhibitors have been promising. Enfuviritide (T20) was the first Food and Drug Administration (FDA) approved fusion inhibitor, which interferes with viral fusion by binding to the viral envelope gp41 [14]. The other is

maraviroc, which is an antagonist at the HIV-1 co-receptor CCR5, and is a useful drug for R5 tropic HIV-1 strain infections [15].

The HIV-core, which contains reverse transcriptase (RT), integrase (IN), and genomic ribonucleic acid (RNA), passes to the cytoplasm of the host cell by leaving its cell membrane on the surface. The genomic single-stranded viral RNA transcribes into double-stranded deoxyribonucleic acid (DNA) with the help of the viral enzyme, RT [16]. The two most important classes of antiretroviral drugs, nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), inhibit RT DNA polymerization and are the cornerstones of HIV treatment.

The viral DNA enters into the host nucleus as nucleic acid-protein complex (pre-integration complex) [17]. Double-stranded viral DNA integrates into the host cell chromosome with the help of the viral enzyme IN [18, 19]. The integrated DNA is now referred to as provirus [17]. Integration marks the shift of the HIV-1 life cycle from the early to late stage [20]. Hereafter, the transcription of proviral DNA mainly depends on cellular transcription factors; however, the viral transcription factor, trans-activator-transcription (Tat), also plays a significant role [17]. Three integrase strand transfer inhibitors (INSTs) are currently approved for use in antiretroviral-naïve patients [21].

Viral DNA is transcribed to messenger RNA (mRNA); different species and sizes of viral mRNA are synthesised. Short mRNA is exported from the nucleus readily while exporting long mRNA, which is unspliced or singly spliced, needs the action of a trans-activating protein [20]. The 9-kilobase of HIV-1 genome has nine genes, which gives about 15

functional proteins. Some of the most important proteins include Gag polyproteins, Pol polyproteins, Env polyproteins, and accessory proteins [22].

The Gag, Env, and Pol polyproteins undergo proteolytic cleavages to provide functional proteins [23]. The accumulation of Gag polyproteins derives the formation of spherical non-infectious immature virion beneath the host cell membrane [24]. The cleavage of Gag polyprotein by the viral protease (PR), results in a mature infectious viral particle. Currently, PR inhibitors (PIs) are one of the most important classes of drugs for the treatment of HIV/AIDS.

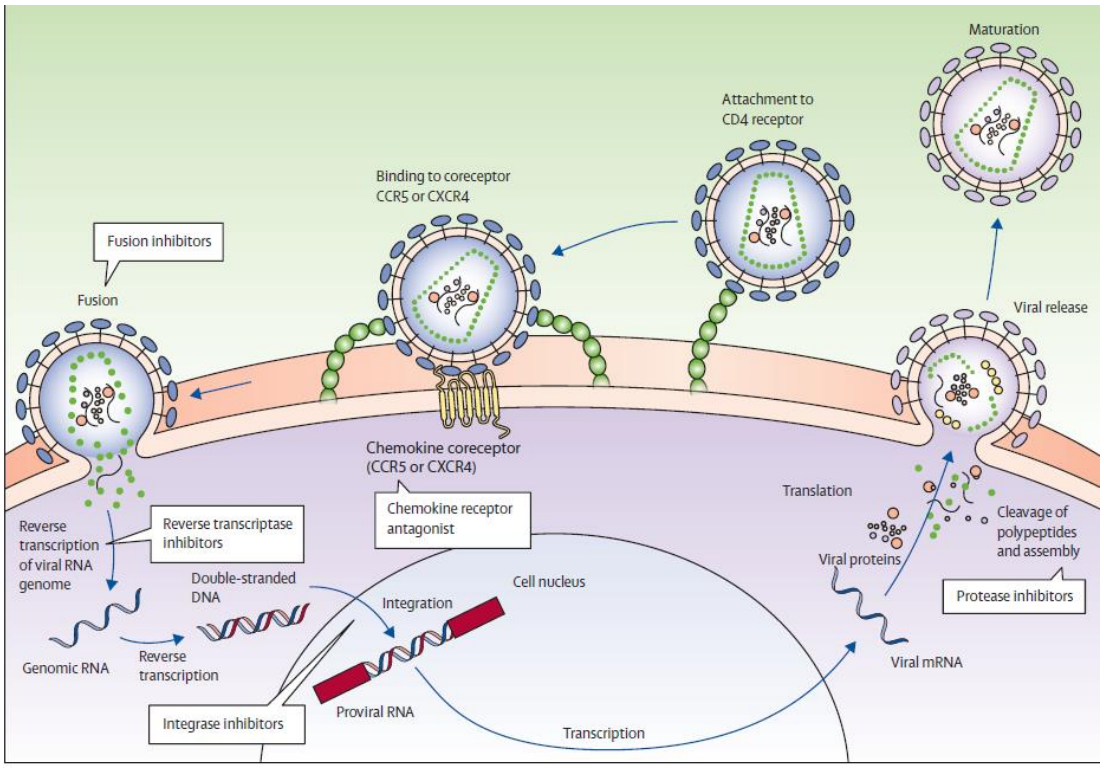


Figure 1. HIV life cycle showing the sites of action of the different class of antiretroviral agents [25].

Acute HIV infection is often symptomatic. HIV-1 infected patients experience an acute retroviral syndrome characterised by clinical signs of immune activation and multi-system dysfunction such as fevers, malaise, and rash. However, these symptoms often go unrecognised [2, 26]. Individuals engaged in unprotected sexual practices or needle sharing at this stage of the infection may transmit HIV [26]. Once these acute symptoms resolve, the infected person passes into an asymptomatic phase of the disease. This stage may persist for several years or rapidly progress to AIDS [26]. As CD4 cell count progressively declines, AIDS-defining opportunistic infections, such as *Pneumocystis jiroveci* pneumonia, Kaposi's sarcoma, and tuberculosis, become common [26]. Adult HIV-infected patients are normally initiated on ART when their CD4 cell count is ≤ 500 cells/μL, or with any symptom indicating a World Health Organisation (WHO) clinical stage 3 or 4, regardless of CD4 cell count [27]. Once treatment is initiated, viral replication is reduced below the threshold where the virus does not evolve, and drug resistance does not emerge, and CD4 cell count increases until it reaches normal levels. The effectiveness of ART inspires efforts toward earlier diagnosis, referral to care, and scale-up of ART. Both CD4 cell count and viral load testing can be conducted using point-of-care testing in HIV-positive patients and are useful to monitor immune system changes and viral replication, respectively [26].

1.3. Antiretroviral therapy

Zidovudine was the first antiretroviral agent shown to provide a survival benefit over placebo in patients with advanced AIDS [28]. However, the use of a single antiretroviral agent did not provide prolonged viral suppression and often did not reverse the decline in immune function [29]. The introduction of PIs into the clinical arena in the mid-1990s and

their use in combination with two NRTIs provided sustained viral suppression and improved immune function [29]. Ever since, the treatment of HIV/AIDS has involved the use of a combination of potent antiretroviral drugs.

In **Figure 1**, there are six major classes of antiretroviral drugs: NRTIs, NNRTIs, PIs, fusion inhibitors, INSTIs, and CCR4 antagonists [26]. The first three classes of antiretroviral drugs are used in combination in resource-limited settings [27]. Only these classes of drugs are reviewed in this thesis. Class, recommended dose, elimination, and common ADRs of these antiretroviral agents are summarised as shown in **Table 1**. Initial regimens for treatment-naïve patients consist of two NRTIs plus a third agent that can be NNRI or 'boosted' PI [27]. The 2013 WHO ART guideline recommended tenofovir plus lamivudine (or emtricitabine) plus efavirenz as a preferred first-line ART regimen for adults, with tenofovir plus lamivudine (or emtricitabine) plus nevirapine or zidovudine plus lamivudine plus efavirenz (or nevirapine) as alternatives. A boosted PI in combination with two NRTIs is recommended as second-line treatment [27].

1.3.1. Nucleoside/nucleotide reverse transcriptase inhibitors

NRTIs are an important class of antiretroviral drugs that are effective in improving both virologic and immunologic outcomes. They are the cornerstone of ART regimens, often referred to as the "backbone" of the regimen [21, 30]. All are prodrugs that need phosphorylation by host enzymes to transform into an active NRTI triphosphate, and competitively inhibit HIV RT to terminate viral replication.

Table 1. Antiretroviral drugs used in resource limited settings.

Drug	Dosing recommendations	Elimination	Adverse drug reactions
Nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs): abacavir, lamivudine, tenofovir, zidovudine, stavudine, didanosine, and emtricitabine.			
Abacavir	300 mg BID, or 600 mg once daily Take without regard to meals.	82% abacavir metabolites excreted renally	Hypersensitivity reaction: patients with HLA-B*5701 gene are at high risk.
Lamivudine	150 mg BID, or 300 mg once daily Take without regard to meals.	Renal excretion: 70%	Minimal toxicity Severe acute exacerbation of hepatitis may occur in HBV-coinfected patients who discontinue lamivudine.
Tenofovir	300 mg once daily Take without regard to meals.	Renal excretion is the primary route of elimination.	Renal insufficiency, Fanconi syndrome, and proximal renal tubulopathy.
Zidovudine	300 mg BID Take without regard to meals.	Metabolised to azidothymidine; which undergoes renal excretion	Bone marrow suppression: macrocytic anaemia or neutropaenia. Nausea, vomiting, headache, insomnia, asthaenia, and nail pigmentation.
Non-nucleoside reverse transcriptase inhibitors (NNRTIs): efavirenz, nevirapine, delavirdine, etravirine, and rilpivirine.			

Drug	Dosing recommendations	Elimination	Adverse drug reactions
Efavirenz	600 mg once daily, at or before bedtime	Metabolised by CYPs 2B6 (primary), 3A4, and 2A6. CYP3A4 mixed inducer/inhibitor (more an inducer than inhibitor) CYP2C9 and 2C19 inhibitor; 2B6 inducer	Neuropsychiatric symptoms, rash
Nevirapine	200 mg once daily for 14 days (lead-in period); after that, 200 mg BID.	CYP450 substrate, inducer of 3A4 and 2B6; 80% excreted in urine (glucuronidated metabolites, <5% unchanged); 10% in faeces)	Rash, including SJS Hypersensitivity reactions, characterised by rash, constitutional findings, and sometimes organ dysfunction (including hepatic failure) reported. Nausea
Protease inhibitors (PIs): atazanavir, darunavir, fosamprenavir, indinavir, nelfinavir, lopinavir, saquinavir, and tipranavir.			
Atazanavir	Atazanavir 300 mg plus ritonavir 100 mg once daily; Take with food	CYP3A4 inhibitor and substrate; and weak CYP2C8 inhibitor	Indirect hyperbilirubinaemia (clinical jaundice), hyperglycaemia, and fat misdistribution.
Darunavir	Darunavir 800 mg plus ritonavir 100 mg once daily Take with food	CYP3A4 inhibitor and substrate CYP2C9 inducer	Skin rash, hepatotoxicity, diarrhoea, and nausea.

Drug	Dosing recommendations	Elimination	Adverse drug reactions
Lopinavir	Lopinavir 400 mg plus ritonavir 100 mg BID, or Lopinavir 800 mg plus ritonavir 200 mg once daily Take without regard to meals.	CYP3A4 inhibitor and substrate	GI intolerance, nausea, vomiting, diarrhoea, and hepatotoxicity.
Integrase strand transfer inhibitor (INSTs): dolutegravir, elvitegravir, and raltegravir.			
Raltegravir	400 mg BID, with rifampin 800 mg BID Take without regard to meals.	UGT1A1-mediated glucuronidation	Rash, Stevens-Johnson syndrome, rhabdomyolysis, myopathy, and myalgia.

BID= twice daily; CYP= cytochrome P450; HLA= human leukocyte antigen; HBV= hepatitis B virus (HBV); UGT1A1= UDP glucuronosyltransferase 1 family, polypeptide A1. Modified from US Department of Health and Human Services (DHHS) Panel on antiretroviral guidelines for adults and adolescents [21].

Most of the NRTIs are eliminated renally and require dose adjustment in patients with renal impairment. Drug interactions are not common in this class of antiretroviral drugs as they are not substrates for cytochrome P450 (CYP) enzymes [31, 32].

1.3.2. Non-nucleoside reverse transcriptase inhibitors

NNRTIs are among the first-line drugs for HIV-1-infected antiretroviral naïve patients in adult ART guidelines [21, 27, 33]. Efavirenz and nevirapine are listed in the recent WHO ART guideline, which was developed for resource-limited settings [27]. NNRTIs induce allosteric changes in HIV-1 RT and prevent viral replication. NNRTIs do not inhibit HIV-2 RT and are not useful in the treatment of HIV-2-infected patients. Unlike NRTIs, NNRTIs are active drugs that do not require sequential phosphorylation to elicit their antiretroviral activity [34].

NNRTIs enhance or inhibit the CYP metabolism of other concomitantly administered drugs [34]. Drugs such as rifampin and rifabutin decrease nevirapine levels and the latter should not be coadministered with these drugs [21]. Class specific rash, hepatotoxicity, drug-drug interactions, efavirenz-associated central nervous system (CNS) disturbances and a low threshold for emergence of resistant mutants are shortcomings of this group of drugs [29].

NNRTIs have a low genetic barrier to the development of resistance; a single mutation to one of the drugs causes high-level resistance to all NNRTIs (except etravirine) [21]. NNRTI-resistant viral strains are common in ART-naïve patients. Genotypic resistance testing is necessary to guide regimen selection before initiation on ART [21].

1.3.3. Protease inhibitors

PIs show their antiretroviral activity by binding to HIV PR and blocking its proteolytic activity, resulting in an inability to form mature infectious virions. Indinavir and nelfinavir use is decreasing as they are associated with intolerable ADRs and pill burden [29]. Similarly, ritonavir is also not used independently as an active antiretroviral agent; instead, at a low dose, it is used in combination with other PIs as a pharmacokinetic enhancer or booster [29]. CYPs metabolise all PIs. Low dose ritonavir (100-200 mg/day) is a potent CYP3A4 inhibitor, and it is used in fixed-dose combination with other PIs to increase their plasma concentration and half-life, allowing their use at lower doses. This results in decreased ADRs and pill burden [21, 29]. PIs have drug interactions with other coadministered drugs that are highly dependent on CYP3A4 metabolism, and caution should be exercised when prescribing [29].

PIs have a high barrier to resistance; they require accumulation of multiple resistance mutations for resistant strains to emerge. The high barrier to resistance makes them an important class of antiretroviral drugs that are effective not only in treatment-naïve patients but also for patients who have experienced treatment failure with other classes of antiretroviral drugs [29]. They are also a preferred category of drugs for patients with adherence concerns, such as patients with a history of poor adherence, active substance users and the homeless [35]. Class-associated ADRs include metabolic abnormalities such as dyslipidaemia and insulin resistance [21].

1.4. Benefits of antiretroviral therapy

ART plays a pivotal role in an AIDS response, reduction in mortality and AIDS-related morbidity, and prevention of HIV transmission. The goal of ending the AIDS epidemic rests on the commitment to provide ART to all who need it, in a right based approach [36]. HIV-positive patients with CD4 counts <200cells/μL are at higher risk of progression to AIDS, non-AIDS morbidity, and mortality than HIV-positive patients with a higher CD4 count [21]. In the early days of recognition of HIV/AIDS, when diagnosis with advanced AIDS was not uncommon, rates of AIDS-related deaths were high, and estimated between 2.1 to 2.5 million people globally as of 2000 [37].

The introduction of widespread HIV treatment has resulted in a dramatic decrease in AIDS-related deaths [5]. In 2014, the number of deaths from AIDS was down to 1.2 million worldwide, of which 790,000 were from sub-Saharan Africa [5]. Effective ART suppresses the viral replication below the limit of detection of the commercially available assay. Durable viral suppression with ART prevents selection of antiretroviral resistance mutations and restores and preserves immune function [26], resulting in a steep decline in the incidence of opportunistic infections [38] and mortality [39]. Life expectancy has increased markedly and returned to the pre-1990s level in high-prevalence countries in sub-Saharan Africa. In South Africa, for instance, life expectancy rose from 52 years in 2005 to 61 years in 2014 [5].

Patients who are initiated on ART at an early stage of HIV infection achieve better treatment outcomes compared to those who commence ART later. Severe *et al*. [40] reported that initiation of ART in patients with a CD4 count between 200 and 350 cells/μL

improved survival, compared with patients who delayed treatment until CD4 counts were <200 cells/μL. Data from a large observational study suggested that initiating ART in patients with CD4 counts between 350 and 500 cells/μL decreased progression to AIDS [41]. In the early stages of HIV infection, viral replication in untreated patients with high CD4 counts was associated with non-AIDS-defining complications such as HIV-associated nephropathy, liver disease, cardiovascular disease, neurologic complications, and malignancies. Sustained virologic suppression delays, prevents or reverses these non-AIDS-defining morbidities [21]. Treatment guidelines are currently recommending an increase in CD4 count threshold for initiation of ART. The recent WHO treatment guideline recommended initiation of ART from 350 to 500 cells/μL [27].

Antiretroviral drugs are effective in the prevention of HIV transmission. Townsend *et al*. [42] reported that only three babies were infected with HIV out of 2,117 infants born to women on ART with viral loads of <50 copies/μL. The HTPN 052 study found that early initiation of ART reduced the rate of sexual transmission of HIV-1 [43]. This study enrolled 1763 couples in which one partner was HIV-1-postive, and the other was HIV-1-negative. A total of 39 HIV-1 transmissions were noticed; 28 were virologically associated with the HIV-infected partner. Of the 28 related transmissions, only one was reported in the early initiated group [43].

1.5. Challenges to antiretroviral therapy

Although there are many benefits of ART, it is also associated with several challenges. These include suboptimal adherence and development of antiretroviral drug resistance and ADRs.

1.5.1. **Adverse drug reactions**

Acute and long-term ADRs are common in patients on ART and have a negative impact on treatment outcomes, including adherence [44-46]. Common ADRs related to ART include gastrointestinal complaints, neuropsychiatric reactions, and skin reactions. Initiation of ART in symptomatic patients improves the quality of life [21]. However, ADRs induced on initiation of ART in asymptomatic patients who are at low risk of AIDS-defining opportunistic diseases may compromise quality of life [21]. For instance, zidovudine-containing regimens that frequently cause severe ADRs such as gastrointestinal complaints and anaemia are still first-line antiretroviral regimens in resource-limited settings [27] and thus have the negative impact on adherence and quality of life of patients [45]. Details of ADRs are described in section 1.6.

1.5.2. Suboptimal adherence

Regardless of CD4 count, patients initiated on ART need to achieve an optimal level of adherence to provide sustained virologic suppression and prevent the emergence of resistant viral strains [21]. ART coverage in adults living with HIV in sub-Saharan Africa has been increasing over the last 15 years; 43% were on ART; 32% were virally suppressed [5], and almost one-third of patients on ART had suboptimal adherence [47].

Adherence is a major predictor of positive treatment outcomes in the management of HIV/AIDS, without which rates of illness and death are high. Besides, perinatal or sexual HIV transmission is more likely in patients with suboptimal adherence [21]. Adherence is discussed in detail in Chapter 2.

1.6. Adverse drug reactions to antiretroviral therapy

ADRs are likely to be detrimental to optimal adherence and successful clinical outcomes [48]. Assessment of ADRs in patients taking ART is becoming increasingly important as HIV transforms into a manageable chronic disease. Long-term achievement of better clinical outcomes needs fine tuning of ART, such as management of ADRs and switching to tolerable regimens [44].

ADRs of antiretroviral drugs are classified based on the organ system affected, as gastrointestinal, neuropsychiatric, skin reactions, and haematological. Each class of ADRs is reviewed below.

1.6.1. Gastrointestinal symptoms

Antiretroviral treatment relates to gastrointestinal complications such as nausea, vomiting, diarrhoea, and gastric discomfort [49]. These symptoms are often underreported and subjective; it is reliant upon clinician interaction and intervention as well as patient awareness and reporting [49]. Gastrointestinal symptoms are among the reasons for discontinuation or switching of ART. Boyle *et al*. [50] reported that of 923 regimens changed over 18 months; 452 (49%) were due to ADRs to ART, and of these 64 (14%) were because of gastrointestinal disturbances.

Ritonavir-boosted PIs and NRTIs, such as zidovudine and tenofovir, are among the inducers of gastrointestinal intolerance [49]. A higher dose of ritonavir is associated with diarrhoea and nausea; currently, only a low dose (100-200 mg/day) of ritonavir is used as a pharmacokinetic booster to other PIs [51]. Atazanavir/ritonavir and darunavir/ritonavir have shown favourable gastrointestinal effects compared to lopinavir/ritonavir [52-54].

The newer generation non-peptidic PI, tipranavir, boosted with ritonavir has shown encouraging gastrointestinal tolerance, similar to darunavir/ritonavir in the POTENT trial [55].

Nausea and vomiting are also associated with NRTI therapy. In the CNA30024 trial, the incidence of grade 2-4 gastrointestinal complaints was high in the zidovudine arm relative to the abacavir arm; nausea was 11% versus 7%, and vomiting was 9% versus 2% when both were taken in combination with lamivudine plus efavirenz [56]. The Gilead 934 study, which compared zidovudine plus lamivudine plus efavirenz with tenofovir plus emtricitabine plus efavirenz, found a slightly higher incidence of gastrointestinal intolerance in the tenofovir arm compared to the zidovudine arm; nausea was 8% versus 6% and diarrhoea was 7% versus 4% [57]. However, in the COMET study, patients switched from zidovudine plus lamivudine plus efavirenz to tenofovir plus emtricitabine plus efavirenz reported significantly less gastrointestinal HIV symptoms [58].

Gastrointestinal complaints are rarely associated with NNRTI therapy. Grade 3 or 4 diarrhoea and vomiting occurred in less than 1% of patients in a randomised controlled trial comparing efavirenz once daily and nevirapine twice daily [59]. The phase III clinical trials, ECHO and THRIVE, reported a higher incidence of diarrhoea in the efavirenz arm (6%) compared with rilpivirine (3%) when each drug was administered in combination with dual-NRTIs [60].

1.6.2. Neuropsychiatric reactions

Neuropsychiatric ADRs are commonly associated with the NNRTIs, especially efavirenz. Staszewski *et al*. [61] reported that more than half of treatment naïve patients initiated on

efavirenz-containing regimens experienced neuropsychiatric disturbances. A review by Shubber *et al*. [62] found that patients taking efavirenz-containing regimens were three times more likely to experience neuropsychiatric ADRs compared to nevirapine-containing regimens. The most common symptoms patients experience within the first weeks include nightmares, dizziness, insomnia, light-headedness, and psychotic symptoms [63]. Some of the efavirenz-induced neuropsychiatric reactions such as depression with suicidal ideation were long lasting, over two years [46, 64].

Studies have reported that 4-10% of patients who experienced short-term neuropsychiatric ADRs of efavirenz discontinued the treatment, mainly within the first 4 weeks [65]. A treatment switch from efavirenz to nevirapine resolves efavirenz-induced neuropsychiatric ADRs [66]. However, adults on nevirapine were twice as likely to discontinue treatment due to any ADRs compared to patients on efavirenz and thus efavirenz-based therapy is the preferred first-line regimen [62].

1.6.3. Skin reactions

A rash is the most common short-term ADR associated with treatment with NNRTIs. Skin reactions commonly related to NNRTIs are erythematous, maculopapular, and extensive [67]. The incidence of skin rash associated with nevirapine ranges from 17% to 32%, although 13% of these were mild in severity[68]. A similar rate of incidence, 14% to 29%, was reported in patients taking efavirenz-containing regimens [69]. Severe rashes such as Stevens-Johnson syndrome and toxic epidermal necrolysis reported in around 6.5% of patients receiving NVP-containing regimens, but less than 1% in NVP-containing regimens

[70].The majority of patients who were taking NNRTIs experienced rash within the first three weeks [67].

A person with preserved immune function has a greater risk of developing the NNRTI-related rash. Women with a baseline CD4 count ≥ 250 cells/μL were more likely to experience the nevirapine-induced rash and hepatotoxicity [71, 72]. Similarly, the risk of developing a skin rash and hepatotoxicity in men with a baseline CD4 count ≥ 400 cells/μL was greater compared to men who had CD4 counts < 400 cells/μL [72]. Racial difference is also a significant risk factor for developing a rash. Thai adults experience skin rash more frequently than white adults [71].

Treatment of nevirapine-induced rash is based on the severity of symptoms. Mild or moderate rashes associated with nevirapine are self-limiting and resolve without nevirapine discontinuation. Severe, grade 3 or 4, rashes such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) require immediate and permanent discontinuation of nevirapine [73]. Similarly, treatment discontinuation is essential for any patient who develops the rash with constitutional symptoms (fever, rigors, and myalgia/arthralgia) involving organ dysfunctions such as hepatitis, eosinophilia, and renal dysfunction [73]. Nevirapine is initiated at 200mg/day for two weeks, and the dose should not be escalated to 400mg/day if the patient experiences a reaction within 14 days [67]. Antihistamines or corticosteroids are useful for the management of skin rash [44]. Topical corticosteroids are more important than oral corticosteroids in the treatment of skin reactions in patients living with HIV/AIDS [74].

1.6.4. Haematological ADRs

Patients initiated on zidovudine-containing regimens experience haematological changes [75]. They can develop bone marrow suppression, the most severe ADR, after three months of zidovudine therapy, which results in anaemia and neutropaenia [76]. The stage of HIV infection, high doses of zidovudine, long durations of treatment, female gender, and background anaemia are important risk factors. The incidences of anaemia and neutropaenia are high in patients having CD4 counts <100 cells/mL. The dose of zidovudine currently used is low, 600mg/day, which decreases the incidence of bone marrow suppression [77, 78]. Firnhaber *et al*. [79] reported that malnutrition and poor economic conditions in Africa and Haiti increased the incidence of anaemia compared to Asia and the USA.

HIV/AIDS patients have been defined as anaemic when their haemoglobin (Hb) level is less than 12 g/dL for men and less than 11g/dL for women [80]. The incidence of anaemia in AIDS patients varies from 1% to 30%, according to AIDS clinical trial group (ACTG) data [77]. Patients in sub-Saharan Africa experience a high incidence of anaemia, for example 50% in the DART trial [81], as a result of deficiencies of micronutrients (e.g. vitamin B12, folic acid, and iron), malaria, and intestinal parasite infections [82, 83]. Zidovudine monophosphate induces anaemia by reducing the phosphorylation of thymidine monophosphate to thymidine triphosphate [84].

Monitoring of HIV/AIDS patients' Hb and haematocrit levels at baseline and during their follow-up helps to avoid development of severe anaemia [77]. Drugs prescribed as prophylactic agents or for treatment of opportunistic diseases (trimethoprim-

sulfamethoxazole, pyrimethamine, and ganciclovir) have synergistic toxicity with zidovudine [77]. Substitution of zidovudine with another NRTI such as tenofovir or abacavir is a feasible option when patients develop anaemia [77]. Previous studies recommended erythropoietin treatment for bone marrow suppression in patients with an erythropoietin level less <500IU/mL [77]. However, many clinical trials reported that the use of recombinant erythropoietin alpha (rHuEPO) did not improve Hb level and the need for blood transfusion compared to placebo, as reviewed by Martí-Carvajal *et al*. [80]. Besides, erythropoietin had shown life-threatening ADRs, such as stroke, and thus its current use is not justified [80].

1.6.5. Other ADRs

NRTIs disrupt oxidative phosphorylation that causes ADRs such as lactic acidosis, hepatic steatosis and hyperlactataemia. Lactic acidosis is a fatal ADR in HIV-infected patients; thus, the cognisance of its signs and symptoms such as fatigue, diminished exercise tolerance, and tachypnoea are necessary for the management [70].

Some ART regimens, especially those containing PIs, are associated with HIV-lipodystrophy syndromes that include dyslipidaemias and insulin resistance [70]. Clinical features of lipodystrophy are fat loss in the face, arms, legs, and buttocks, and fat accumulation in the intra-abdominal area, dorsocervical spine, and breasts. Metabolic features include hypertriglyceridaemia, hypercholesterolaemia, and insulin resistance [67].

I have highlighted the important class of antiretroviral agents and their ADRs that are currently available for treatment of HIV/AIDS in resource-limited countries. The next

chapter revised literature about adherence to ART in sub-Saharan Africa in general and Ethiopia in particular.

CHAPTER TWO

2. ADHERENCE TO ANTIRETROVIRAL THERAPY: LITERATURE REVIEW

Adherence and compliance are interchangeably used terms in the literature to describe the medication taking behaviour of a patient. However, slight differences have been perceived [85, 86]. Medication compliance refers to the degree to which patients' medication taking behaviour matches with healthcare providers' recommendations. The term "compliance" fails to describe patients' involvement to establish a treatment plan and thus its use is declining [87]. Cramer *et al.* [88] defined medication adherence as "the act of conforming to the recommendations made by the provider on timing, dosage, and frequency of medication taking." The word "adherence" suggests the patient has active, voluntary, and collaborative participation in establishing the treatment plan, and many health providers prefer the term "adherence" to "compliance" [85].

Active suppression of viral replication to prevent the emergence of drug resistance requires achievement of more than 95% adherence to ART [89]. Current regimens that contain boosted PIs or NNRTIs can achieve good viral suppression at a lower level of adherence. Boosted PIs reach a higher plasma concentration compared to unboosted PIs, which extends their biological half-life. Thus, boosted PIs are more "forgiving" of non-adherence than unboosted PIs. Furthermore, PIs have a high barrier to the development of drug resistance. These properties make regimens containing boosted PIs a treatment of choice for possibly non-adherent patients [35].

2.1. Measure of adherence

Monitoring of patients' medication-taking behaviour has been practised since the time of Hippocrates, when the efficacy of different remedies was documented with notations of whether the patients had taken medication or not [87]. Even in the modern era of medication therapy, patient self-report is a widely used measure of adherence to medicines [90]. Despite the fact that antiretroviral medication adherence is crucial for exploiting their full potential, there is no 'gold standard' method to measure adherence [87].

Methods for adherence measurement can be classified as direct and indirect. Direct methods such as directly observed therapy (DOT), and measuring the level of drug or its metabolite in plasma and other body fluids confirm the intake of the drug. Indirect methods such as self-report, pill count, pharmacy records, electronic devices, and biological markers do not prove drug ingestion [87, 91]. The advantages and disadvantages of these methods are reviewed below.

2.1.1. Patient self-report

Self-reported measures of adherence (questionnaires, diaries, interviews or visual analogue scales) commonly use a single item query regarding missed doses in a particular period. The patient is asked about the number of prescribed doses that have been missed in the last 1, 3, 4, 7 or 30 day(s) [92, 93]. Researchers have used different items for assessing self-reported adherence; there is no standard tool. Furthermore, in some studies investigators included additional items that assess patients' adherence on the weekend, taking the dose with a specified schedule, and to food and fluid restrictions [93]. An adherence index which amalgamated time and food adherence with dose adherence had a

stronger correlation with viral load than adherence measured using a single item of dose in adherence questionnaire [94].

Advantages of self-reported adherence measures include convenience, simplicity, feasibility, inexpensiveness, accuracy for identifying non-adherers, and ability to collect evidence regarding dose scheduling as well as food and fluid restrictions [92, 95]. As a result of the above merits, they are widely applied in research and clinical settings in both resource-rich and resource-limited countries [93].

Self-reported adherence correlates with pill count, medication event monitoring systems (MEMS), pharmacy refills, and biological markers. Simoni *et al.* [92] reported that viral load was associated with self-reported adherence in 88% of recall periods that were greater than 3 days and in 64% of those that were 3 days or less, χ^2 (N=63)=4.16, p=0.04. Similarly, CD4 count was correlated with self-reported adherence in 62% (16/26) of studies [92].

Self-report overestimates adherence 10-20% more than objective methods such as MEMS [96]. Social desirability and recall bias are the reasons mentioned behind the overestimation [95, 96]. Experts advise on using different techniques to decrease adherence overestimation, such as saying that non-adherence is a common phenomenon, approaching the client with non-judgmental wording, asking open-ended and forced multiple choice items, asking about missed doses, asking about the most recent doses, and helping patients to remember [92, 93].

It is crucial to consider the optimal recall period for assessment of self-reported adherence, as the frequency of dosing of antiretrovirals is now once or twice daily. Too few doses can be assessed in a very short period (i.e. 1-3 days), and the variability of adherence behaviour

may not be sufficiently observed [89]. Lu *et al*. [97] compared 3, 7, and 30-day self-report recall periods with MEMS and found that 30-days showed less overestimation of adherence than the 3 or 7-day recall periods [97]. The 7-day recall period is advantageous over 1, 3, and 4-day period as this time includes a weekend, during which patients may miss medications [92].

2.1.2. Pill count

Pill count is an objective method for measurement of adherence. It is one of the most common methods next to self-report [98]. Similar to self-report, pill count also overestimates adherence and over-adherence (>100%) is not uncommon. Percentage adherence is calculated as the total number of pills taken during the study period divided by the total number of tablets that should have been taken multiplied by one hundred [99]. Over-adherence can be because pills are lost, vomited, given to someone or dumped, while considered as ingested [99]. Pill count may promote distrust between the healthcare provider and the patient if patients believe counting as distrust in their medication adherence [91].

To avoid patients' pill dumping some researchers have used an unannounced pill count in which patients were not informed about the precise date of counting and counting is usually done by pill counters in patients' homes. Unannounced pill count is more reliable than announced pill count, but it lacks feasibility as it costs time and money and some patients may consider it as an invasion of privacy [91, 99].

2.1.3. Pharmacy records

Some studies have used pharmacy records to measure adherence to antiretroviral drugs [100, 101]. The principal premise of this method is that refilling of medication with time is considered as a sign of good adherence [93, 102]. Patients who do not refill medication are either missing medication or not taking the medication at all. This method has limitations, as medication refill does not indicate actual ingestion of the drugs. Also, if patients have access to the drug through other means (i.e. free samples, family members, or friends) or from other pharmacies, this method is invalid. Pharmacy records are a convenient method when patients receive the antiretroviral drug from the same pharmacy [91, 93, 102]. Adherence from the pharmacy refill is determined by equating the real to expected refill dates [102].

Some of the merits of pharmacy refill compared to self-report include it being immune to social desirability and recall bias, and pill dumping. It also allows census analysis of adherence as data are easily obtained from pharmacies [102]. Data from pharmacy refill have been moderately correlated with clinical outcomes [103]. However, Townsend *et al*. [104] reported no significant association between medication refill and viral load or CD4 count.

2.1.4. Electronic drug monitoring

Electronic drug monitoring (EDM) is the most unconventional means to measure adherence to medications [91]. It uses a pill bottle with a cap embedded with an electronic chip that records the opening date and time of the cap. The information stored in chips is transferred onto a computer [93, 102]. EDM captures patterns of both dose and time

adherence; it is considered as a gold standard method to measure adherence [102, 105]. Several studies have used EDM to measure adherence in patients with antiretroviral drugs and to validate other instruments for adherence measurement [105-107].

EDM can decrease overestimation of adherence by avoiding pill dumping and the "white coat effect" (better adherence before a visit to a physician). Several limitations of this method have been identified including taking out several doses in one bottle opening, opening a bottle without removing a dose, the lack of a guarantee of dose ingestion, and monitoring using EDM on its own is an adherence intervention [102, 105]. One of the most common types of EDM is the medication event monitoring system (MEMS); however the cap is sizeable, cumbersome and not suitable for patients that use pill boxes and non-oral dosage forms [91, 102].

Haberer *et al*. [108] used a wireless pill container (Wisepill®) for monitoring medication adherence in patients on antiretroviral drugs in Uganda. Wisepill transmits a cellular signal upon opening to remove medication. It has provided a capacity to control adherence proactively and can prevent treatment failure and the emergence of viral resistance.

2.1.5. Therapeutic drug monitoring

Determining the concentration of a parent drug or its metabolite in plasma, urine and saliva can be unequivocal proof of the ingestion of medication. This method only assesses adherence of patients over 24 hours; few doses can be determined in this short period. Besides, patients may take medication just before their appointment - i.e. display "white coat adherence" [109]. Podsadecki *et al*. [109] showed that 66% of the patients had perfect

adherence 1-3 days before pharmacokinetic sampling based on the plasma concentration of lopinavir in patients taking tenofovir plus emtricitabine plus lopinavir/ritonavir [109].

Individual and racial difference in the pharmacokinetics of the drug may also affect the amount of drug available in the plasma [110, 111]. Drug-drug and drug-food interactions may similarly result in variations in plasma drug concentration [112]. Therapeutic drug monitoring suffers from a lack of quality control of the assay. Methods of specimen collection, cross-validation of determination of drug level, and interpretation of test readings vary between different settings [102, 112].

2.1.6. Other measures

Changes in a surrogate marker when patients are initiated on ART have been mentioned in the literature as a useful measure of adherence. The increase in mean corpuscular volume is suggested to monitor adherence of patients on zidovudine or stavudine therapy. Levels of plasma uric acid and bilirubin can be used to measure adherence in patients taking didanosine and indinavir therapy, respectively [93].

2.2. Adherence to ART in sub-Saharan Africa

The concern that sub-Saharan Africa patients, many of whom live in poverty and with a lack of formal education, may not achieve an optimal level of adherence to ART has been waning over the past decade. A meta-analysis by Mills *et al.* [113] found that 77% of patients (95% Confidence Interval (CI), 68%-85%) met the threshold for optimal adherence in African studies (27 studies; 12,116 patients in total) compared to 55% (95% CI, 49%-62%) in North American studies (31 studies; 17,573 patients in total). The latest meta-analysis by Ortego *et al.* [47] also reported that 67% (95% CI, 56%-79%) of patients

were optimally adherent in sub-Saharan Africa studies, which was still higher than 59% (95% CI, 53%-65%) and 62% (95% CI, 59%-66%) in North American and worldwide studies, respectively.

Access to ART in the sub-Saharan Africa has been improving and has transformed HIV/AIDS into a chronic disease. However, only two-thirds of patients achieved optimal adherence [47]; hence, there is a growing interest in and recognition of the importance of identifying issues associated with long-term adherence to ART to improve adherence and treatment outcomes. Adherence to medication is a dynamic behaviour influenced by many factors. Overall factors associated with adherence to antiretroviral medication can be classified into three subgroups: patient-related factors, healthcare system-related factors, and regimen related-factors [114]. The influences of these factors on adherence to ART in sub-Saharan Africa patients are elaborated on in the following sections.

2.2.1. Patient-related factors

Demographic characteristics such as gender, age, marital status, religion, and ethnicity have been inconsistent predictors of adherence across studies. Being male has been significantly associated with both optimal [115, 116] and suboptimal adherence [117-120]. Maqutu *et al.* [116] reported that the rate of adherence was significantly higher in males than in females at the beginning of follow-up, but this difference disappeared at the end of the 17th months (17th follow-up visit). Several other studies [121-127] did not find an association between gender and adherence to ART.

Increasing age was associated with better adherence in all studies that found age as a significant predictor of adherence [115, 126, 128-132]. For instance, being aged 18-24, 25-

34 and 35-44 vs. ≥44 (OR=2.00, 95% CI=1.05-3.83; OR=2.51, 95% CI=1.50-4.20; OR=2.06, 95% CI=1.28-3.30, respectively) were independently associated with higher odds of 30-day non-adherence [126]. Studies have reported a lack of association between marital status [115, 117, 119-122, 126, 131, 133-138], ethnicity [121, 135, 139], and religion [115, 117, 121, 138-140] with adherence.

Socioeconomic status, as indicated by education, employment status, income, food insecurity and transport costs, has been shown to influence adherence to ART in sub-Saharan Africa. Most of the studies that evaluated the level of education have not found an association with adherence [117-120, 122, 126, 131, 136, 139-145]. Those studies that had reported significant association found inconsistent relationships. Eholie *et al*. [125] reported that attaining secondary school education or above was associated with suboptimal adherence. No schooling was related to optimal adherence to ART among HIV-positive patients in South Africa [116]. A study in a Nairobi slum on patients taking on ART found a low level of education as an independent predictor of suboptimal adherence. This study reported that 62% of patients achieved optimal adherence [135].

Six studies reported no significant relationship between employment status and adherence to ART [117, 120, 129, 139, 142, 145]. Significant but inconsistent relationships were reported for unemployment in two studies; being unemployed was associated with suboptimal adherence in a survey of 253 Nigerian HIV-positive patients who had been on ART for a minimum of 6 months [115] while unemployment was related to optimal adherence in Cameroonian HIV-positive patients [140]. Several studies have assessed the relationship between income and adherence, but only one study found a significant

association. Low income was predictive of suboptimal adherence in treatment naïve Cameroonian HIV-positive patients initiated on ART [118].

Findings have also been inconsistent in describing the association between adherence and food insecurity. Berhe *et al*. [141] reported that malnutrition was about 10 times more frequent in Ethiopian patients with suboptimal adherence. Food insecurity independently predicted suboptimal adherence in Congolese patients taking ART [145]. On the contrary, Sasaki *et al*. [119] reported experiencing food insufficiency in the past 30 days was associated with optimal adherence. This might be due to the greater social support focusing on people living in extreme poverty.

Psychological problems are related to suboptimal adherence in HIV-positive patients taking ART. A high level of depression was related to suboptimal adherence in all studies that reported depression as a significant predictor of adherence [124, 143, 146-150]. Do *et al*. [124] found that the presence of depression in Botswanan patients taking ART was associated with suboptimal adherence. Nakimuli-Mpungu *et al*. [142] reported that psychological distress (depression and anxiety) and living alone were independent predictors of suboptimal adherence in Ugandan HIV-positive patients.

Thirteen studies [124, 126, 129, 133, 140, 146, 147] reported a negative association between adherence to ART and alcohol use or disorders. Jaquet *et al*. [133] reported that alcohol consumption was significantly associated with lower adherence in HIV-positive patients in Western Africa. Etienne *et al*. [146] reported that alcohol use in the last month was predictive of poor adherence in HIV-infected patients from five different sub-Saharan Africa countries.

Social supports that may involve emotional and material support for patients taking ART play a significant role in improving adherence. Consistent significant findings define the positive relationship between social support and adherence [128, 149, 151]. Diabate *et al*. [128] reported that absence of social support was related to suboptimal adherence. Peltzer *et al*. [149] found that a higher social support score was associated with achieving optimal adherence. Tiyou *et al*. [152] found that family support was related to better overall adherence (dose, time, and food). Encouraging patients to disclose their HIV status to family and friends, who can provide social support, facilitates medication taking.

Disclosure of HIV status relates to adherence to ART. Two studies reported that failure to disclose HIV status decreased adherence to ART [124, 135]. Do *et al*. [124] reported that failure to disclose one's HIV-1 status to a partner was predictive of suboptimal adherence. Unge *et al*. [135] found that not disclosing HIV status (OR=4.7, 95% CI=1.78-12.43) was significantly associated with dose adherence of < 95%. Five studies [119, 129, 137, 145, 153] did not find an association between disclosure of HIV status and adherence. Some patients may not disclose their HIV status due to fear of stigma and discrimination. Stigma and discrimination were barriers to adherence to ART in sub-Saharan HIV-positive patients [147, 154]. Dlamini *et al*. [154] reported that perceived stigma was significantly associated with self-reported missed medications.

The use of memory aids such as mobile phone text-message reminders and pill boxes facilitate adherence to ART [144, 151]. Studies trialling the effect of mobile phone text-message reminders in sub-Saharan African HIV-positive patients found a significant improvement in adherence in the intervention group [155, 156].

Patients' baseline clinical parameters such as WHO or Centers for Disease Control and Prevention (CDC) clinical stage of HIV/AIDS, CD4 count, viral load, and weight did not predict adherence in several sub-Saharan African studies [116, 118, 121, 125, 127, 136, 137, 139, 149, 152, 153, 157]. Significant but inconsistent relationships were found between adherence and baseline CD4 count in two studies. CD4 count ≥250 cells/μL was associated with lower adherence in Western Africa HIV-positive patients [128] while CD4 count < 350 cells/μL was related to poor adherence in Ethiopian HIV-infected patients [141]. Berhe *et al.* [141] reported that having a baseline BMI < 18.5 kg/m^2 was associated with poor adherence to ART.

2.2.2. Healthcare system-related factors

Healthcare system-related factors, including quality of care, patient engagement, and patient satisfaction, are important determinants of adherence. Etienne and collaborators [146] showed that perceived high quality of care was highly correlated with adherence. In another study, Watt *et al*. [131] found that lower perceived quality of patient-provider interaction was associated with poor adherence. Munene *et al*. [138] showed that higher patient engagement in HIV care services was correlated with optimal medication adherence. However, Ukwe *et al*. [144] did not find significant correlations between trust in HIV care providers and patient satisfaction with the level of care with adherence.

Structural factors that directly relate to the healthcare system such as transport difficulties influence adherence. Taiwo *et al*. [158] found that HIV-positive patients initiated on ART and living <20km from the clinic were significantly more likely to have >95% adherence than those living >100km from the hospital. Being resident in the urban area, where

patients have better access to HIV care service and thus pay lower transport costs and travel shorter distances, was associated with optimal adherence [116, 149]. However, the relationship is not consistent; Alakija *et al*. [115] reported that increasing distance to the hospital and transport fare were positively correlated with adherence.

The structural barriers to clinic attendance scale score, which was developed by Coetzee and Kagee [159], was significantly associated with poor adherence to ART [120]. Improving healthcare accessibility increased patients' adherence to ART. Moshabela *et al*. [160] reported that patients referred from hospital-based programmes to primary healthcare centres in rural South Africa were more likely to feel respected by healthcare providers, less liable to complain of long queues, perceived lower stigma, and showed a better level of ART adherence than the hospital-based users.

2.2.3. Regimen-related factors

Regimen-related factors such as pill burden, dosing frequency, ADRs, regimen type, and dietary and fluid restrictions are important determinants of adherence to ART. Inconsistent findings are reported on the impact of pill burden on adherence to ART. Three studies [124, 137, 145] did not find a significant association between pill burden and adherence. Falang *et al*. [129] reported that lower pill burden was associated with higher adherence in Nigerian HIV-infected patients taking ART. Diabate *et al*. [128] showed that the 10 or more daily pills was predictive of poor adherence to ART. In earlier studies, frequent dosing was not uncommon; Orrell *et al*. [132] showed that three times daily dosing predicted incomplete adherence and virologic failure.

Studies have investigated the impact of ADRs on adherence to ART. Some of the studies found that ADRs were significant barriers to adherence [122, 126, 150]. Reporting severe ADRs in the past 30 days was associated with higher odds of non-adherence [126]. Denison *et al*. [137] reported experiencing more HIV and ADRs symptoms was related to incomplete adherence. Three studies did not find an association between ADRs and adherence to ART [118, 134, 139].

Significant but inconsistent relationships were reported for duration of ART and adherence across studies; longer duration of ART was associated with higher adherence in Kenyan patients taking ART [138] while it was associated with lower adherence in Senegalese patients [127]. Eholie *et al*. [125] also showed that being on ART for equal to or greater than 12 months was associated with suboptimal adherence.

Adherence is significantly different among regimens containing different classes of antiretroviral drugs. Patients on a PI-based regimen have been shown to have lower adherence compared to patients taking a NNRTI-containing regimen [127]. Patients taking different antiretroviral drugs of the same class have also shown different adherence rates. Peltzer *et al*. [149] reported that patients on nevirapine-containing regimens had better adherence compared to those taking efavirenz-containing regimens. Denison *et al*. [137] also showed that patients taking non-nevirapine-containing regimens achieved lower adherence compared to those on nevirapine-containing regimens. However, other studies did not find a significant association between ART regimen and adherence [118, 125, 140, 146, 157]. Some ART regimens require dietary and fluid restrictions. Regimens that did not have such restriction have been associated with optimal adherence [134].

There is a lack of consistency in the sub-Saharan African literature in relation to several of the factors identified above. These inconsistencies may correlate with a difference in culture, research methodology and quality of healthcare services across countries. Further research identifying the broad range of factors that lead to non-adherence in sub-Saharan Africa are necessary for developing evidence-based interventions aimed at individuals with suboptimal adherence to ART. This recommendation was also shared by Ortego *et al*. [47] in a meta-analysis of 84 observational studies. The efficient use of scarce antiretroviral drugs in resource-limited countries requires a comprehensive report on the wider range of biological and psychosocial factors involved. The lack of comprehensive studies in the case of Ethiopia is described in section 2.3.

2.3. HIV/AIDS and its management in Ethiopia

2.3.1. HIV/AIDS and treatment scale-up in Ethiopia

According to the 2007 census, Ethiopia's population was estimated at 74 million, the second largest population in sub-Saharan Africa nexA to Nigeria, and it grew at an average annual rate of 2.6% between 1994 and 2007. Eighty-four percent of the population was rural. Around 45% of the Ethiopian population was under the age of 15 [161].

Ethiopia is one of the sub-Saharan African countries hardest hit by the HIV epidemic. HIV probably began to spread in Ethiopia about three decades ago [162]. HIV was detected for the first time in Ethiopia in stored sera collected in 1984 [163] and the first AIDS cases were reported in 1986 in Yikatit 12 Hospital, Addis Ababa [164]. HIV prevalence in the 1980s was very low; however it increased at an alarming rate in the 1990s [162]. It reached its peak of about 4.5% between 1998 and 2000. There was significant variation in

urban and rural prevalence, 14% and 2.5%, respectively, as shown in **Figure 2** . The epidemic stabilised in cities between 1996 and 2000, and in rural areas between 1998 and 2000 [163]. In 2003, the total number of HIV/AIDS patients was estimated to be between 1.5 and 2.3 million [165]. As in other sub-Saharan Africa countries, new HIV infections have been declining in Ethiopia [166]. According to the 2011 Ethiopia Demographic Health Survey (EDHS), overall HIV prevalence in adults (15-49 years) was 1.5%.

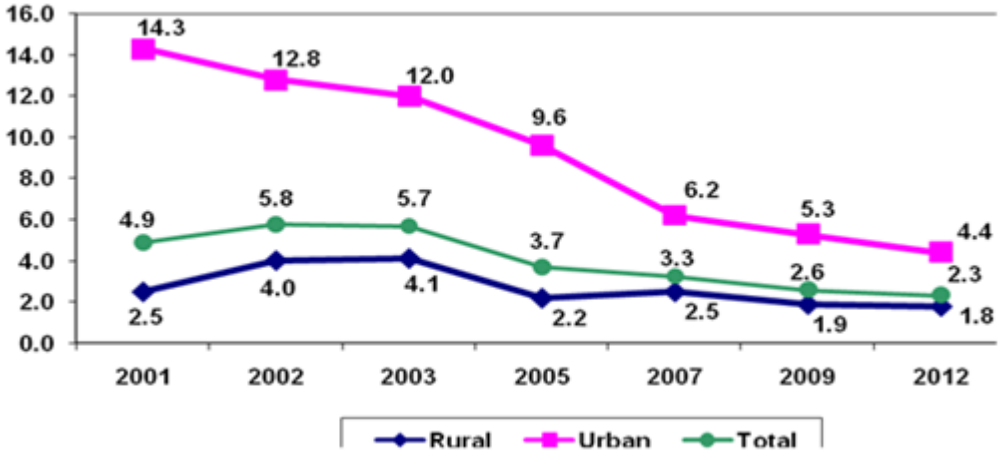
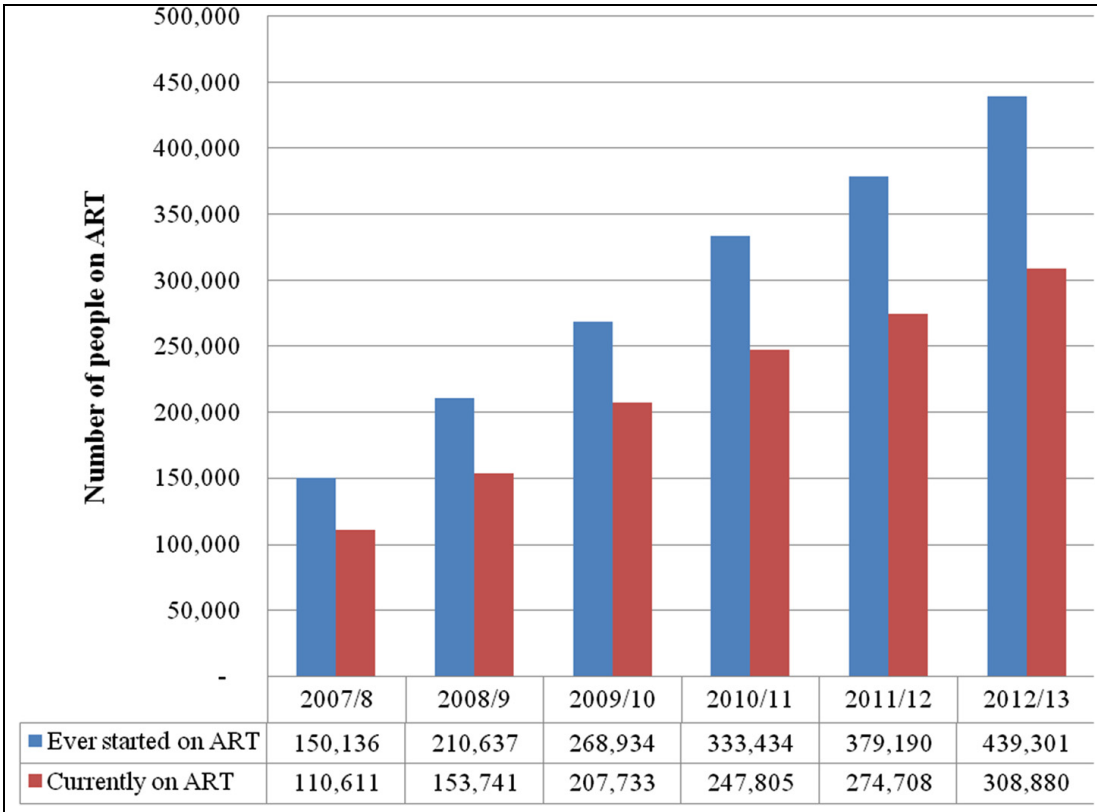


Figure 2. Trends in HIV prevalence among Ethiopian antenatal care clients in urban and rural sites, 2001-2012 [167].

The scale-up of free ART services has been one of the best achievements that the country has witnessed in its health sector. The number of facilities providing the treatment had been expanded from three as of 2005/2006, when free treatment launched, to 913 as of 2012/2013 [167]. AIDS-related deaths decreased substantially following the scale-up of ART. The number of people receiving ART in Ethiopia increased from less than 9,000 in 2005 to more than 439, 000 in 2013 as shown in **Figure 3** [168]. The total number of adult patients receiving treatment in Ethiopia was 339,043 as 2014 [169]. The overall adult treatment coverage of those in need has reached 65%. However, 30% of patients ever

initiated on ART are not retained in care and this indicates the challenges in providing ART services in Ethiopia [167].



	2007/8	2008/9	2009/10	2010/11	2011/12	2012/13
Ever started on ART	150,136	210,637	268,934	333,434	379,190	439,301
Currently on ART	110,611	153,741	207,733	247,805	274,708	308,880

Figure 3. Trends of the number of people receiving ART in Ethiopia, 2007-2013 [168].

2.3.2. Factors associated with adherence to ART in Ethiopia

Given that this research project focused on HIV/AIDS management in Ethiopia, it was important to have a comprehensive understanding of the issue in this country. Seventeen studies that evaluated the predictors of adherence in Ethiopian HIV/AIDS adult patients were identified in this review. A total of 5,190 participants were involved in the studies. Characteristics of the studies are summarised in Table 2. Among the studies included, 12 were cross-sectional studies (n=4,288) [147, 150, 152, 170-178], three were qualitative

studies (n=154) [179-181], one was a case-control study (n=348) [141], and one a prospective study (n=400) [151].

Table 2. Characteristics of Ethiopian studies.

Study	Sample	Setting	Study design	Cut-off points for adherence	Number adherent	% adherent	Adherence measure
Tsega et al. 2015 [173]	351	Gondar Hospitals	Cross-sectional	100%	284	80.9	Pill count
Ketema et al. 2015 [175]	422	Debrebrihan Hospital and Debrebrihan Health Centre	Cross-sectional	100%	403	95.5	Self-report
Lifson et al. 2015 [178]	22	Arba Minch Hospital	Qualitative				
Mitiku et al. 2013 [174]	239	Harari Hospitals	Cross-sectional	≥95%	208	87	Self-report
Berhe et al. 2013 [138]	348	Mekele, Suhul, St. Marry, and Adwa Hospitals	Case-control	≥95%	174	50	Not reported
Negash et al. 2013 [144]	355	Addis Ababa	Cross-sectional	≥95%	261	73.5	Not reported
Mengistu et al. 2012 [167]	420	Addis Ababa Hospitals	Cross-sectional	Not reported	308	73.3	Not reported

Study	Sample	Setting	Study design	Cut-off points for adherence	Number adherent	% adherent	Adherence measure
Kebede et al. 2012 [170]	24	Dawuro Hospital	Cross-sectional	100%	8	33.3	Self-report
Gusdal et al. 2011 [176]	118	Ethiopian urban hospitals; Ugandan urban and rural hospitals	Qualitative				
Balcha et al. 2011 [177]	14	Bishoftu, Mojo, and Sebeta	Qualitative				
Giday A et al. 2010 [168]	510	Hawassa Hospital	Cross-sectional	≥95%	450	88.2	Self-report
Tiyou et al. 2010 [149]	319	Jimma Hospital	Cross-sectional	≥95%	303	95	Self-report
Tessema et al. 2010 [171]	504	Gondar and Felege Hiwot Hospitals	Cross-sectional	100%	231	45.8	Self-report
Beyene et al. 2009 [172]	422	Yirgalem, Hawassa, and Shashemene Hospitals	Cross-sectional	≥95%	393	93	Self-report/Pill count
Amberbir et al. 2008 [148]	400	Jimma Hospital	Prospective cross-	≥95%	384	96	Self-report

Study	Sample	Setting	Study design	Cut-off points for adherence	Number adherent	% adherent	Adherence measure
			sectional				
Markos et al. 2008 [172]	291	Yirgalem Hospital	Cross-sectional	100%	287	98.6	Self-report /pill count
Tadios Y et al. 2006 [147]	431	Addis Ababa	Cross-sectional	≥95%	350	81.2	Self-report

The studies were published between 2006 and the present. Eight of the studies were published before 2012 and the rest in or after 2012 (when this project commenced). Most of the studies published in or after 2012 suggest there is an increasing interest in issues associated with adherence in Ethiopian patients.

All except three of the quantitative studies [141, 147, 170] have reported on the adherence measure used. Most [141, 147, 150-152, 170-174, 177, 178] evaluated adherence using self-report, asking patients about the number of missed doses over a particular period. The overall adherence rate using self-report was 80%. Only three studies [172, 175, 176] used pill account as the adherence measure, two of them with self-report[172, 175]. Beyene *et al*. [172] reported an adherence level of 88%, while a 2015 study [176] found a lower rate of adherence of 81%. All qualitative studies [179-181] involved patients taking ART in addition to caregivers or peer counsellors in interview or focus group discussions; the rates of adherence in these groups of patients were not reported. Seven quantitative studies [141, 147, 150-152, 170-175, 177, 178] used ≥ 95% adherence as the cut off point for optimal adherence while five studies [173-176, 178] grouped patients as optimally adherent when patients did not miss any dose in a specified time.

Sixteen individual themes relating to barriers to adherence were acknowledged in this review. Patient-related barriers include unemployment [171, 172, 176], depression [147, 151, 174], low level of education or knowledge [171, 173], stigma and discrimination [147, 170], alcohol use [147, 172], malnutrition [141], failure to disclose HIV status [172], lack of social support [172], non-readiness to commence ART [174], not having a life project [174], having a dependent [175], and younger age [176]. Regimen-related barriers including taking zidovudine/stavudine-containing regimen or

experiencing ART-related ADRs [150, 172, 174, 175], frequent dosing [172], and use of complementary and alternative medicines [178] were identified. Distance from the healthcare facilities [175] was the only healthcare system-related barrier identified.

Eight themes regarding facilitators of adherence were identified. The two most important facilitators identified were an active relationship with the healthcare provider [150, 170, 173] and social support [152, 172, 178]. The remaining facilitators were identified only in single studies, and included the use of memory aids [151], fitting regimens with daily routines [150], diagnosis of late stage HIV/AIDS [152], better family income [152], being male [152], and disclosure of HIV status [176].

Overall, the previous studies conducted in Ethiopia have many weaknesses. Most of the studies were cross-sectional and assessed limited variables at one point in time; they therefore had limited ability to capture changes in adherence behaviour. Only one prospective study of three months' duration evaluated the levels of adherence and factors that hinder or facilitate adherence to ART. More rigorous evaluations of associations reported by cross-sectional studies using long-term prospective methodologies are required as suggested by Mann *et al*. [182]. Previous qualitative studies mainly focused on exploring factors influencing patient retention at the healthcare level and were limited in their ability to examine barriers to, and facilitators of, medication adherence at the individual level.

2.4. Justification for the current study

As discussed above, studies previously conducted among Ethiopian HIV-positive patients taking ART have several limitations. In general, they have lacked the evaluation of the level of adherence and its determinants required to provide comprehensive information to design effective ART interventions in the Ethiopian setting.

This study used mixed methods research methodology including a prospective study and exploratory qualitative research to identify barriers to, and facilitators of, adherence to ART. It was carried out in two hospitals involving HIV/AIDS patients, nurses, and case-managers. The triangulation using the different methodologies deepens our understandings of problems associated with HIV/AIDS treatment. ADRs are common in patients' initiated on ART and are important issues in the management of ART. However, only a few retrospective studies have attempted to identify ADRs in Ethiopian patients' initiated on ART. We examined the incidence and nature of ADRs, identified the risk factors associated with the development of ADRs, and assessed their impact on adherence. Given the evolution of therapy over time and unresolved questions regarding what 'optimal adherence' actually means, a meta-analysis was performed to determine the relationship between the cut-off point for optimal adherence to ART and virologic outcomes. As access to ART is progressively improving, the results of this study will aid policy makers and HIV care managers to develop efficient strategies to improve treatment outcomes in Ethiopian HIV/AIDS patients.

CHAPTER THREE

3. ADHERENCE TO ANTIRETROVIRAL DRUG THERAPY IN ADULT HIV-POSITIVE PATIENTS IN NORTHWEST ETHIOPIA: A STUDY PROTOCOL.

3.1. Abstract

Introduction: Achievement of optimal medication adherence and management of antiretroviral toxicity pose great challenges among Ethiopian patients with HIV/AIDS. There is currently a lack of long-term follow-up studies that identify the barriers to, and facilitators of, adherence to antiretroviral therapy (ART) in the Ethiopian setting. Therefore, we aim to investigate the level of adherence to ART and a wide range of potential influencing factors, including adverse drug reactions (ADRs) occurring with ART.

Methods and analysis: We are conducting a 1-year prospective cohort study involving adult patients with HIV/AIDS starting on ART between December 2012 and March 2013. Data are being collected on patients' appointment dates in the ART clinics. Adherence to ART is being measured using pill count, medication possession ratio, and patient's self-report. The primary outcome of the study will be the proportion of patients who are adherent to their ART regimen at 3, 6 and 12 months using pill count. Taking 95% or more of the dispensed ART regimen using pill count at given points of time will be considered the optimal level of adherence in this study. Data will be analysed using descriptive and inferential statistical procedures.

Ethics and dissemination:

Ethics approval was obtained from the Tasmania Health and Medical Human Research Ethics Committee and Bahir-Dar University's Ethics Committee. The results of the study will be reported in peer-reviewed scientific journals, conferences, and seminar presentations.

Article summary

Article focus

To establish the level of adherence and identify factors that influence adherence to ART in Ethiopian HIV/AIDS patients in a cohort study.

Key messages:

Factors that affect adherence to ART have not yet been identified in Ethiopian HIV/AIDS patients in a long-term follow-up study.

Data obtained during this prospective cohort study over the period of at least of 12 months will identify important factors associated with long-term adherence to ART that will assist in optimising the outcomes of Ethiopian HIV/AIDS patients.

Strength and limitations of this study

This study will identify factors that affect adherence to ART in treatment naïve patients who are initiated on ART with long-term follow-up.

Rates of patient drop out, loss to follow-up and death are high in this setting, which may challenge the success of the project.

3.2. Introduction

Ethiopia is home to approximately 800,000 patients with HIV/AIDS and the prevalence of HIV/AIDS in the general population is estimated to be 1.5% [183]. The free antiretroviral therapy (ART) program in Ethiopia, introduced in 2005, has decreased mortality and morbidity, and improved the quality of life of patients [184]. In the past 8 years, decentralisation and scale-up of the HIV care program has occurred, and by the end of 2011, 249,174 adult patients (86% of eligible patients) were on ART [185].

Achievement of optimal medication adherence, management of antiretroviral drug-related toxicities, and patient retention [174, 186] are becoming the greatest challenges in the management of HIV/ADS in Ethiopia. A cross-sectional study of Ethiopian patients reported an adherence rate of 88.1% [172], which is below the near perfect adherence (≥95%) required to maintain the effectiveness of ART [187].

Patient retention in HIV care facilities is low, and averaged 51% to 85% in 55 Ethiopian HIV care facilities in a 2-year patient follow-up study [186]. Similarly, a 2011 report from the Ethiopian Ministry of Health indicated that patients dropping out from HIV care was a serious issue, with up to 40% of patients who started ART dropping out from treatment in some regions of the country [188]. Mortality and drop out from treatment are most common in the first year of patient follow-up in Ethiopia [189].

Adherence to medication is a dynamic behaviour affected by factors related to treatment regimen complexity, patient-related variables, patient-health care provider relationships, and the quality of health care services [190].Patient adherence to ART is also influenced by regimen-related factors such as pill burden, frequency of dosing, adverse drug reactions (ADRs), and fluid and dietary restrictions[191]. Similarly, patient-related factors such as lack of transport, shortage of food, use of traditional

medicine, alcohol abuse, depression, stigma and discrimination, and lack of social support undermine adherence [192-195]. Further, a poor patient-health care provider relationship and low quality services, such as lack of confidentiality and privacy, and drug stock outs can hamper adherence with ART[192].

3.3. Justification for this study

Previous studies were retrospective cross-sectional studies, lacked active surveillance and did not focus on treatment naïve HIV/AIDS patients. While one prospective study has investigated adherence to ART in Ethiopia [151] it was only conducted for three months and also did not focus on treatment naïve patients. A prospective study with a longer follow-up focusing on treatment naïve patients is required to assess the level of adherence in this patient group and its barriers and facilitators. There is also a need to conduct a prospective study in Ethiopian patients with HIV/AIDS to assess the emergence of ADRs to ART in clinical practice, and the potential relationship between ADRs and non-adherence to ART.

3.4. Objectives

The objectives of this study are to establish the level of medication adherence and identify factors that influence medication adherence, and assess the incidence of ADRs and associated risk factors in Ethiopian patients with HIV/AIDS initiated on ART.

3.5. Methods and analysis

3.5.1. Study design

This study is a prospective cohort study in which adult Ethiopian patients with HIV/AIDS initiated on ART are being followed from the time of ART initiation (Month (M) =0) to 12 months of therapy (M=12). ART-initiated patients have an appointment

every month for six months and every three months thereafter in ART clinics in Ethiopia; research pharmacists will collect data on appointment dates. The timeline of data collection activities is structured as shown in **Table 3**. The sequencing and repeating of measures is to observe the time pattern of different predictors on adherence to ART in treatment naïve patients. Depression, stigma, HIV-treatment knowledge, healthcare relationship, and belief about medication, and HIV-symptom index may affect adherence in a time-dependent manner and are being measured before and after 6 months of patients' ART using validated scales. Data regarding the concomitantly administered medications, comorbidities, ADRs, and laboratory values are collected on every appointment date.

Table 3. Time line of data collection.

Data	Time point								
	Baseline	**M1**	**M2**	**M3**	**M4**	**M5**	**M6**	**M9**	**M12**
Socio-demographics	√								
HIV treatment knowledge	√							√	
Social support			√						√
Substance abuse	√								
Depression (CES-D)			√					√	
Berger-stigma			√					√	
Self-report adherence				√			√	√	√
Pill count			√	√		√	√	√	√
Pharmacy record review				√			√	√	√
Self-reported HIV symptoms (HSI)				√			√	√	√
Beliefs about medication (BMQ)			√					√	
Health care relationship				√					√
Patient experience of ADRs for the last 4 weeks		√	√	√	√	√	√	√	√
Patient's medical record review	√			√			√	√	√

3.5.2. Study setting

The project is being carried out in two hospitals in Northwest Ethiopia: Gondar University Hospital and Felege-Hiwot Hospital. Each hospital has 400 beds and serves a catchment area of 5 million people. The total number of HIV/AIDS patients attending each hospital is approximately 7,000 and 10,000 at Gondar University Hospital and Felege-Hiwot Hospital, respectively. Recruitment into the study occurred between

December 2012 and March 2013. The study will continue to March 2014, which will allow a follow-up period of at least 12 months for each patient.

3.5.3. Inclusion / Exclusion criteria

All HIV/AIDS patients at least 18 years old and being initiated on ART for the first time, are invited to participate. Patients whose follow-up was to be conducted in other hospitals, rather than at the hospital where ART was initiated, are not included.

3.5.4. Sample size

The sample size for this study was determined based on a previous study, where 76% of patients had optimal dose, time, and food adherence to ART [151].Taking a 95% confidence level, and precision of 0.07, the sample size was estimated to be 143.

Based on an average of 43 new patients per month, within four months of recruitment in each ART clinics the pool of patients for recruitment will be 344. Allowing for a non-participation rate of 23%, and loss to follow-up of up to 30% (Mekides B and Desalew K, July 2012, personal communication), the sample size is achievable.

3.5.5. Recruitment

Between December 2012 and March 2013, participants were initially invited by their nurses to participate in this study. At the first visit (usually two weeks before ART initiation), nurses gave patients information about the study and invited them to participate. If patients were interested in participating in the study, the research pharmacists contacted them to discuss the research. Informed consent was obtained from volunteer participants using a standard information statement and consent form. Each participant receives $US 3 to reimburse their time and transport cost. The

characteristics of patients who declined participation were collected to determine the representativeness of the sample.

3.5.6. Measures

The questionnaires have been spread to track changes of the different parameters over time as shown in **Table 3**, while minimising questionnaire fatigue. Assessment of adherence is a problematic issue as there is no gold standard method of measurement [91]. In this study self-report, pill count and Medication Possession Ratio (MPR) will be used to measure adherence at months 3, 6, 9, and 12. Use of multiple measures of adherence is recommended in literature as there is no single optimal measure of adherence [91]. Adherence to medication found using multiple measures will be converted into 'percentage dose adherence' and triangulated. For example, self-reported percentage adherence over 30 days will be triangulated with percentage dose adherence obtained using pill count over the same duration, which will be useful to estimate patients' true medication adherence. Percentage adherence to each of the medications will be calculated and the lowest dose adherence taken as the adherence for a given patient.

The primary outcome of the study will be the proportion of patients who are adherent to their ART regimen at 3, 6 and 12 months using pill count. The optimal level of adherence in this study will be considered as taking 95% or more of the dispensed ART regimen using pill count at a point in time. Adherence from pill counts will be calculated by dividing the difference between current and previous pill counts by the number of pills that have to be taken during the same period [172]. Pill counts have been found to be an economic and reliable measure of adherence in resource-limited settings [196].

A modified AIDS Clinical Trial Group (ACTG) self-reported adherence questionnaire that asks patients how many doses they missed in the last 7 days has been used to measure patients' dose adherence to ART. In addition, two four-item modified questionnaires from the ACTG have been used to measure time and food adherence in the last 7 days [90]. Assessing multiple dimensions of adherence by using all items of the ACTG self-reported adherence questionnaires has provided a strong measure of adherence [94]. Self-reported adherence is well correlated with viral load suppression and is particularly suitable for resource-limited settings because of its low cost [92].

Patients stating they have missed medication will be asked to indicate reasons for nonadherence from a list of 16 reasons (e.g. away from home, busy with other things, simply forgot). Fourteen of the reasons for non-adherence are taken from the ACTG [90] and two reasons associated with traditional medicine and religious treatment, respectively, were obtained from literature review [193].

Pharmacy refill records have been reviewed and the MPR will be calculated by dividing the total number of days covered with the medication dispensed by the number of days between the first fill and the last refill plus the days' supply of the last refill [197]. This method is suitable in our study as HIV-medication is refilled only from the nearby governmental hospital/health centre pharmacy in Ethiopia [185]. Pill count and MPR are superior to self-reported adherence measures and well correlated with virological failure and clinical outcomes [198]. Biological surrogate markers such as viral load and CD4 count correlate with medication adherence [199]. The CD4 count is measured every 6 months in ART clinics; the measures at months 6 and 12 will be used as a biological surrogate marker of adherence. Viral load is not routinely measured in Ethiopian clinical practice, and so has not been included in the trial protocol.

Depression in patients is being evaluated using the seven-item questionnaire of the Center for Epidemiological Studies Depression (CES-D) scale. This scale has been extensively applied in different settings, including in HIV/AIDS patients [90]. The Revised Berger HIV stigma scale has been used for measurement of stigma. The 10 items of the Berger stigma scale have been validated in HIV-positive youth [200]. The Berger stigma scale was also used in Kenyan patients with HIV/AIDS [201]. A higher score indicates the existence of greater stigma [202].

Previous studies have suggested that a lack of social support predisposes patients with HIV/AIDS to medication non-adherence [203]. Patients' satisfaction with the social support they get from family members and friends and the help of the support for remembering their medication has been measured using two four-point scale social support questionnaires [90].

The HIV treatment knowledge scale has been used to measure patients' knowledge on adherence, ADRs and drug resistance. This instrument has been developed and validated by Balfour et al. [204] in HIV/AIDS patients taking ART.

The BMQ has been used to measure patients' beliefs about ART. The BMQ consists of two five-item scales probing patients' beliefs about the necessity of the given medication and their concerns about possible ADRs [205, 206].

The trust between the patients and health care providers has been measured using the 13-item HCR trust scale. Items are rated from 0 to 4; the total score ranges from 0 to 52 and a higher score indicates a greater level of trust [207].

A Self-completed HIV Symptom Index (HSI) is used to measure patients' concern about 20 possible symptoms associated with ART ADRs. The research pharmacists are

interviewing patients, their caregivers and physicians, and referring to patients' medical records and documenting detailed information regarding the adverse effects that patients experience. The severity of ADRs has been rated using the WHO ADR severity scale [208]. Similarly, a physician and a pharmacist have been determining the causality of each ADR using Naranjo's probability scale [209]. The reliability between raters and within raters has improved significantly ($p<0.001$) with the use of Naranjo's probability scale [209].This scale has been widely used in various settings [210]. In addition, the Schumock and Thornton scale has been used to rate the preventability of adverse drug events [211].

Socio-demographic and economic variables such as age, gender, marital status, religion, level of education, number of children, employment status, disclosure of HIV status, average number of meals per day, monthly income, transportation costs to the clinic, and waiting time in the hospital are collected at the baseline.

Laboratory data such as weight, height, history of ADRs, hepatitis B virus (HBV) and hepatitis C virus (HCV) infection status, WHO stage of HIV/AIDS, CD4 count, haematocrit, white blood cell (WBC) count, absolute neutrophil count, platelet count, liver function tests [alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), and bilirubin direct and total], renal function tests [such as blood urea nitrogen (BUN), serum creatinine, and urea], and ART regimen, date of initiation, dose and frequency of treatment, other concomitant medications and comorbidities have been recorded from patients on each appointment date from their medical records using a clinical and laboratory data collection sheet.

'Non-persistance' from ART program is defined as patients not presenting for refilling of their ART for the last 3 months. Patients' record will be used to calculate the number of

days covered by the last dispensed HIV medication and 90 days will be added to determine the date when patients are categorised as 'non-persistances'. The characteristics of study subjects who do not make at least 6 months follow-up (non-persistent patients) will be examined separately and compared with those who are persistent. It helps to determine the potential impact of attrition bias on the validity of our findings. Patients lost the follow-up are being tracked by peer counsellors working in the ART clinics of both hospitals using the registered address and phone number of them or their family member or close friend in their medical record. The reason for being lost to follow-up has been recorded. Socio-demographic and clinical prognostic characteristics of those lost from the treatment, and those continuing ART will be compared.

The percentage of missing items for each scale will be calculated for each participant. If more than 10% of the items of the scale are missed, the patient's total score on that scale will be excluded from data analysis at that time point. The proportion of missing participants for each variable of interest will be calculated.

3.5.7. Statistical analysis

Descriptive univariate analysis will be conducted for socio-demographic and economic variables. Adherers will be compared with non-adherers with the Pearson chi-squared test for categorical variables and independent samples t-tests for normally distributed continuous data. Similarly, the characteristics of patients who developed ADRs and did not develop ADRs will be compared using Pearson chi-squared tests for categorical variables and independent samples t-test for continuous variables. Risk factors for adherence will be determined by investigating the influence of socio-demographic, socio-economic variables, and psychosocial variables, healthcare provider relationship,

beliefs about medications and ADRs. Risk factors for ADRs will be determined by investigating the effects of gender, age, body mass index (BMI), CD4 count, history of drug allergy, comorbidities, concomitant medications, and type of regimen. Multiple variable binary logistic regression will be used to evaluate the independent influence of these risk factors on adherence. The exposure and the potential confounders will be modelled in relation with the outcome variable for adjustment using a multiple-predicative regression model. The final model will be determined after checking multicollinearity. All statistical calculations will be performed using SPSS Version 21.0 (IBM Corp., New York, USA). A p-value of <0.05 will be considered as statistically significant.

3.6. Quality control

The English-speaking native researcher made the forward translation of the validated questionnaires into Amharic. Two physicians working in the ART clinics of the Ethiopian hospitals reviewed the developed Amharic versions. A professional translator made the backward translation to check the difference between the Amharic versions and the original English versions. The differences between the source version and target version were settled by a meeting of the forward translator, a physician and the back-translator, and final Amharic versions were developed. The Amharic version was pretested with 40 adult patients receiving ART who would not be included in the main study to check for reliability and validity of the questionnaires. Items found to be problematic by patients were modified.

3.7. Data management

The investigators have been checking the collected data for completeness, accuracy and clarity. These checks have been performed daily after data collection and amendments

have been made before the next data collection point. Data clean up and crosschecking have also been done prior to data analysis. The research pharmacists have been assessing the severity [208], causality [209], and preventability [211] of adverse events separately using validated algorithms.

The data have been entered from the two study sites in Ethiopia into a custom-built website housed on a secure server at the University of Tasmania. Stored data have been backed up on a daily basis. Access to the information has been only granted to authenticated investigators from anywhere using the Internet.

The custom-built website generates data collection forms for printing. After completion these forms have been scanned and then uploaded to the website. The data from the forms have been entered onto the website by the research pharmacists. A random sample of the scanned forms has been checked against the website data to ensure accuracy. Additionally, the website has a sophisticated series of checks to ensure that fields are entered and that all fields are within expected values. Researchers at each site have been informed of any incomplete or inconsistent data.

3.8. Strengths of the study

Several features in the design and planning of the project contribute to the strengths of the study. First, the study is intended to examine predictors of adherence from different perspectives including patient characteristics, medication regimens, and the health care system. Patients' socio-economic status, level of education, belief and knowledge of HIV medication, social support and psychosocial variables are mentioned as predictors of adherence elsewhere [212, 213].

Second, the study uses multiple measures of adherence, which is recommended in the literature as there is no gold standard method of adherence measurement [91].

Although patients in sub-Saharan Africa have been reported to have a comparable rate of adherence with those in the developed countries [113], there is a plausible explanation in the literature that studies in sub-Saharan Africa measure adherence mainly using self-report, which overestimates adherence by as much as 20% [96]. Patients refill their HIV-medication in a specific government ART clinic pharmacy; this allows us to use pill count and pharmacy records for adherence measurement [91, 93, 102].

3.9. Limitations of the study

Rates of patient drop out, loss to follow up and death are high in this setting [189], which may challenge the success of the project. The multiple measures of adherence used in the study may alter patients' behaviour and overestimate medication adherence [214] (i.e. Hawthorne effect).

The study period may not be sufficient to document long-term ADRs, such as endocrine and metabolic adverse events, which may need more than one year to become apparent. Patients may not show up in ART clinics for treatment of ADRs or may be treated in other nearby clinics, which may underestimate the incidence of ADRs.

3.10. Ethics and dissemination

Ethics approval was obtained from the Tasmania Health and Medical Human Research Ethics committee (Approval Number: H0012722); and Bahir Dar University's Ethics Committee (RCS/567/2004). Nurses working in the ART clinics familiarised patients with the study; research pharmacists delivered further information to interested participants. Participants were given the chance to read and understand the information sheet and to ask any questions before providing written consent. Copies of the information sheet and consent form were handed on to study participants who

consented. All personally identifying information has been removed from the questionnaires and study documents. Study participants have been identified only using a unique study number. The hardcopy data will be stored in a locked filing cabinet in the Bahir Dar University premises for 5 years; afterwards the data will be shredded and disposed of in secure bins. Access to the filing cabinet and custom-built website will only be granted to authenticated investigators. We will disseminate our findings via a public presentation to stakeholders working on HIV/AIDS treatment in Ethiopia. The results of the study will be reported in peer-reviewed scientific journals, conferences, and seminar presentations.

3.11. Conclusion

The study is expected to provide extensive information about adherence, including the barriers to and facilitators of adherence, and the ADR profile among a cohort of Ethiopian patients commencing on ART. This will establish an important foundation for a subsequent intervention study focussing on improving adherence in ART naïve patients with HIV/AIDS.

CHAPTER FOUR

4. ANTIRETROVIRAL ADHERENCE AND TREATMENT OUTCOMES AMONG ADULT ETHIOPIAN PATIENTS

4.1. Abstract

Developing appropriate strategies to sustain optimal medication adherence among the increasing number of HIV-positive patients taking antiretroviral therapy (ART) in sub-Saharan Africa is a major challenge. The objective of this study was to determine patient, regimen, disease, patient-provider, and healthcare-related factors associated with adherence with ART over a one-year period, and assess the impact of adherence on treatment outcomes. We performed a prospective, observational study among 246 patients who were initiated on ART in Ethiopia. Of 172 who completed follow-up, 130 (75.6 %) had ≥ 95 % self-reported adherence. In multivariate analyses, lower BMI (OR 1.2; 95 % CI 1.0, 1.4) and HIV symptoms distress scores (OR 0.9; 95 % CI 0.9, 1.0) and the use of medication reminder devices (OR, 9.1; 95 % CI 2.0, 41.6) were associated with higher adherence. CD4 count increase was significantly higher in the adherent patients compared to non-adherent patients at 12 months (159 cells/μL [Interquartile range (IQR), 72-324 cells/μL] vs. 132 cells/μL [IQR, 43-190 cells/μL]; p = 0.026, Mann-Whitney U test). Our findings indicate that interventions aimed at improving adherence and thereby treatment outcomes in patients initiated on ART should promote the use of reminder devices, and monitor HIV symptoms and adverse reaction distress and nutritional status.

Keywords Antiretroviral therapy, highly active; Medication adherence; HIV; Treatment outcomes; Ethiopia

4.2. Introduction

At the end of 2013, 12.9 million people were on antiretroviral therapy (ART) worldwide. Of these 11.7 million (90.7 %) were living in low-and middle-income countries [215]. Since 2005, when a free ART programme was launched in Ethiopia [184, 188], decentralisation and scale-up of the programme has occurred and a total of 270,460 adult patients were receiving ART by 2012 [167]. ART has resulted in a dramatic decrease in mortality and morbidity in patients with HIV/AIDS [216]. Although studies have reported that less-than-perfect adherence (< 95 %) to non-nucleoside reverse transcriptase inhibitor (NNRTI)-containing regimens can lead to viral suppression [217, 218], near perfect adherence (≥ 95 %) to ART achieves better virological and treatment outcomes [219]. Furthermore, it is recognised that non-adherence to treatment can lead to insufficient viral suppression and promote the emergence of drug-resistant viral strains, resulting in regimen failure, clinical progression to AIDS, and death [220, 221].

Medication adherence to ART changes over time [222]. Previous studies have identified regimen and disease-related factors, healthcare-related factors, psychological factors, and knowledge and belief about treatments as being associated with non-adherence [223, 224]. Only a few studies (three cross-sectional studies and a three-month follow-up study) that assessed limited variables at a single time point have been performed in Ethiopia [150-152, 172]. There was a need for a multicentre longitudinal study to assess a wide range of factors potentially associated with long-term adherence among adult HIV-positive patients initiated on ART. The objective of this study was therefore to identify key determinants of adherence with ART over a one-year period, and to compare treatment outcomes between adherent and non-adherent patients.

4.3. Methods

This was a prospective cohort study of treatment-naïve adult (≥ 18 years) HIV/AIDS patients recruited from Felege-Hiwot and Gondar University Hospitals, Northwest Ethiopia, from December 2012 through March 2013. Details of the study setting have been described elsewhere [225]. Nurses and research pharmacists recruited participants from hospitals. Written informed consent was obtained from each participant for their participation. Patients were followed for 12 months after initiation of ART. All patients who attended 12 months' follow-up and had complete self-reported adherence data were included in this analysis.

4.3.1. Measures

Details of the questionnaires and the time-line of administration have previously been described [225]. Patients' sociodemographic (e.g., gender, age) and socioeconomic (e.g., level of education, employment status) information was self-reported at the study baseline. Clinical data (e.g., CD4 count, weight) were obtained from patients' medical charts every month for the first six months and every three months thereafter. The chart schedule switched to fit with patients appointment in the ART clinics.

Dose and time adherence was measured using the modified AIDS Clinical Trial Group (ACTG) self-reported adherence questionnaire [90]. The questionnaire was administered every three months. Dose adherence was assessed by asking patients how many doses they had missed in the last 7 days, and calculated as the percentage of prescribed doses actually taken over that period. Similarly, time adherence was assessed by asking participants how closely they followed their specific medication time in the past 7 days, using a 5-point Likert scale, ranging from "never" to "all the time"; the score was converted to percentage time adherence. Means of dose and time adherence

were taken as a combined indicator of ACTG self-reported adherence. Clinic-based pill count, 30 day visual analogue scale (VAS), and medication possession ratio (MPR) measures were also carried out at the same time for comparison. Details of adherence measures have previously been described [225]. Adherence in this study was the combined self-reported dose and time ACTG measured adherence at 12 months. Optimal adherence in this study was defined as achieving 95 % or more in combined self-reported dose and time adherence at 12 months.

4.3.1.1. Healthcare relationship

The trust between the patients and healthcare providers was measured using the 13-item Healthcare Relationship (HCR) scale. Items were rated from 0 to 4; the total score ranged from 0 to 52 and a higher score indicated a greater level of trust [207, 226]. Reliability for the HCR scale in this sample was 0.94 using Cronbach's alpha.

4.3.1.2. HIV treatment knowledge

The HIV treatment knowledge scale was used to measure patients' knowledge on adherence, adverse drug reactions, and drug resistance. This instrument was developed and validated by Balfour et al. [204] in patients with HIV/AIDS. Cronbach's alpha in this study was 0.50.

4.3.1.3. Beliefs about medicines

The Beliefs about Medicines Questionnaire (BMQ) was used to assess patients' beliefs about ART [206]. The BMQ measures perceived necessity of ART (8 items) and perceived concern about potential adverse drug reactions (11 items). Necessity-Concern Differential (NCD) was calculated by subtracting concern scores from necessity scores, and used as a numerical indicator for rating patients' perceived need of treatment to concern about taking medication [205, 206]. Reliability was good for BMQ

necessity and concern subscales (0.71-0.78) in the sample. Cronbach's alpha for the whole BMQ scale in this sample was 0.68.

4.3.1.4. HIV Symptoms and ADR distress

The HIV-Symptom Index (HSI) [227] was used to measure distress associated with HIV symptoms and ADRs. It included a 20-item scale where participants were asked if they had experienced each of the listed symptoms (e.g., nausea, headache) during the past four weeks. Participants rated on a 5-point Likert-type scale (0 = I do not have this symptom, 4 = It bothers me terribly) the extent to which the symptoms bothered them. The HSI had good internal consistency in this sample (Cronbach's alpha 0.85).

4.3.1.5. Depression

The Centre for Epidemiological Studies Depression scale (CES-D) [228] assessed frequency of seven depressive symptoms over the past week. It employs a 4-point Likert-type scale ranging from 0 = never/rarely to 3 = mostly or always. It has been extensively applied in different settings, including in patients with HIV/AIDS [90]. CES-D had good internal consistency in this sample; with Cronbach's alpha of 0.81.

4.3.1.6. Stigma

Stigma was assessed using the revised 10-item version Berger Stigma Scale [200], which consist of four subscales: Personalized Stigma, Disclosure Concerns, Negative Self-Image and Public Attitudes. Participants could answer on a 4-point Likert-type scale ranging from 1 = strongly disagree to 4 = strongly agree. For each subscale, item scores were added to provide a personalized stigma score ranging from 0 to 12, a disclosure concern score ranging from 0 to 8, a negative self-image score ranging from 0 to 12, and public attitudes score ranging from 0 to 8. The whole Berger Stigma scale had good internal consistency (Cronbach's alpha 0.90).

4.3.1.7. Substance use

The Alcohol Use Disorder Identification Test (AUDIT-C) has two questions about alcohol use; the number of days on which the patients had alcohol-containing drinks in last 30 days and the amount of alcohol drinks consumed on the days when they did drink alcohol [229]. Cronbach's alpha for AUDIT-C in this sample was 0.65. Questions about the use of khat, a shrub whose fresh leaves and shoots are chewed for psychostimulant effects [230], in the past 6 months were also collected.

4.3.2. **Statistical analysis**

Characteristics of adherent (adherence at 12 months ≥ 95 %) versus non-adherent (< 95 %) patients were compared using independent sample t-tests for normally distributed continuous variables; Mann-Whitney U tests for ordinal (Likert-type scales) and non-normally distributed continuous variables; and chi-square or Fisher's exact tests (cell size less than 5) for nominal variables. Variables with a p value of ≤ 0.2 on univariate analysis were included in the logistic regression model. Two-sided assumptions and tests were adopted for all statistical readings. $P < 0.05$ was used as the threshold of statistical significance. Analyses were performed using SPSS, version 22 (IBM Corp., New York, USA).

4.4. Results

4.4.1. **Study participants**

From December 2012 to March 2013, 347 HIV-positive individuals were screened; 337 adults (≥18 years; 191 females and 146 males) initiated on ART at the two sites and 246 (72.9 %) patients (143 females and 103 males) were enrolled in this study. There were no significant differences in the WHO clinical stage of HIV/AIDS, gender, age, CD4 count,

and weight between subjects who did and did not participate in the study. One hundred and seventy-two (69.9 %) participants who completed 12 months' follow-up were included in this analysis. Seventy-four (30.1 %) were excluded from analysis: 15 were lost to follow-up, 17 withdrew from the study, 15 died, 12 transferred to other ART clinics, and 15 did not complete 12 months' follow-up. There were no significant differences in gender, age, CD4 count and weight at baseline between those who did and did not complete 12 months' follow-up. Patients who had WHO clinical stage III/IV HIV/AIDS at baseline were twice more likely to not complete 12 months' follow-up. One hundred and four (60.5 %) patients were female, and the median age of patients included in the analysis was 32 years [Interquartile Range (IQR), 27-40]. The median CD4 count at treatment initiation was 185 cells/μL [IQR, 95-253] and 85 (51.5%) participants were diagnosed with stage III or IV HIV/AIDS based on WHO clinical staging criteria. The median income per month was 400 Ethiopian Birr (~20 USD), and the median travel time to the clinic was 30 minutes. At enrolment visit, 136 (79%) patients had their own mobile phone among them 87 (64%) patients could be able to send and receive a text-message.

Table 4. Participant characteristics.

Characteristic	Total (%) (n=172)	Adherent patients (n=130)	Non-adherent patients (n=42)	Odds Ratio (95 % CI)	P value
Demographics					
Gender (female)	104 (60.5)	81 (62.3)	23 (54.8)	1.37 (0.68-2.76)	0.491
Age, median years (IQR)	32 (27-40)	32 (28-40)	30 (25-40)	-	0.228
Married	99 (57.6)	73 (56.2)	26 (61.9)	0.79 (0.39-1.61)	0.634
Completed secondary school or above	83 (48.3)	69 (53.1)	14 (33.3)	2.26 (1.09-4.67)	0.041
HIV treatment knowledge score, median (IQR)	19 (17-20)	19 (17-20)	18 (17-19)	-	0.035
Parents living with children	113 (65.7)	84 (64.6)	29 (69.0)	0.82 (0.39-1.73)	0.735
Ethiopian Orthodox Christian	157 (91.3)	118 (90.8)	39 (92.9)	0.76 (0.20-2.82)	0.478

Characteristic	Total (%) (n=172)	Adherent patients (n=130)	Non-adherent patients (n=42)	Odds Ratio (95 % CI)	P value
Disclosure of HIV status to:					
Spouse	87 (50.6)	69 (51.5)	20 (47.6)	1.17 (0.58-2.35)	0.792
Offspring	49 (28.5)	40 (30.8)	9 (21.4)	1.63 (0.71-3.72)	0.332
Parents	34 (19.8)	23 (17.7)	11 (26.2)	0.61 (0.27-1.4)	0.327
Siblings	23 (13.4)	13 (10.0)	10 (23.8)	0.36 (0.14-0.89)	0.043
Relatives	27 (15.7)	19 (14.6)	8 (19.0)	0.73 (0.29-1.81)	0.658
Friends	24 (14)	17 (13.1)	7 (16.7)	0.75 (0.29-1.96)	0.743
Socioeconomic characteristics					
Employed	79 (45.9)	65 (50)	14 (33.3)	2.0 (0.97-4.14)	0.088
≥ 2 meals per day	138 (82.1)	107 (84.3)	31 (75.6)	1.73 (0.73-4.07)	0.307
Monthly income, median ETB* (IQR)	400 (100-1000)	400 (100-1000)	400 (100-1000)	-	0.682
Transport cost, median ETB* (IQR)	5 (3-20)	4.5 (3-20)	7.5 (2-20)	-	0.928

Characteristic	Total (%) (n=172)	Adherent patients (n=130)	Non-adherent patients (n=42)	Odds Ratio (95 % CI)	P value
Travel time to clinic, median min (IQR)	30 (20-60)	30 (20-60)	30 (15-67.5)	-	0.714
Disease and medication-related variables					
Body-mass index, median kg/m2 (IQR)	19.5 (18.0-22.1)	19.7 (18.1-22.6)	19.0 (17.7-20.7)	-	0.117
Weight, median kg (IQR)	52 (47-57)	53 (47-57.8)	50 (45-56)	-	0.051
CD4, median cells/μL (IQR)	185 (95-253)	188 (94.5-260.5)	162.5 (95.5-248)	-	0.387
WHO HIV/AIDS clinical stage III & IV	85 (51.5)	61 (49.6)	24 (57.1)	0.74 (0.36-1.5)	0.505

Characteristic	Total (%) (n=172)	Adherent patients (n=130)	Non-adherent patients (n=42)	Odds Ratio (95 % CI)	P value
HIV symptom index score, median (IQR)	3 (0-6)	1 (0-4)	5 (2.3-15.5)	-	<0.001
Zidovudine-based regimen	86 (50)	68 (52.3)	18 (42.9)	1.46 (0.73-2.95)	0.375
Nevirapine-based regimen	71 (41.3)	60 (46.2)	11 (26.2)	2.4 (1.12-5.21)	0.035
Dosing once daily	79 (45.9)	57 (43.8)	22 (52.4)	0.71 (0.35-1.43)	0.431

* ETB – Ethiopian birr

Table 5. Psychosocial and healthcare system-related factors associated with ACTG adherence.

Variables	Total (%) (n=172)	Adherent patients (n=130)	Non-adherent patients (n=42)	Univariate analysis Odds Ratio (95 % CI)	P value	Multivariable analysis Odds Ratio (95 % CI)	P value
Depression score ≥ 3	18 (10.5)	10 (7.7)	8 (19.0)	0.35 (0.13-0.97)	0.046	0.9 (0.2-4.9)	0.906
Berger stigma score, median (IQR)	2.2 (1.4-2.4)	2.1 (1.3-2.3)	2.3 (2.2-2.5)	-	<0.001	0.9 (0.3-3.0)	0.896
Personalized stigma score, median (IQR)	2 (1-2)	2 (1-2)	2 (2-2)	-	<0.001	-	-
Disclosure concerns stigma score, median (IQR)	2.5 (2.5-3)	2.5 (2.5-3)	2.5 (2.5-3)	-	0.277	-	-
Negative self-image stigma score, median (IQR)	2 (1-2)	2 (1-2)	2 (2-2.8)	-	<0.001	-	-
Public attitudes stigma score, median (IQR)	2 (1-2.5)	2 (1-2.5)	2.5 (2.4-3)	-	0.001	-	-
Substance use							
AUDIT-C score ≥ 4	21 (12.2)	15 (11.5)	6 (14.3)	0.78 (0.28-2.17)	0.840	-	-
Khat use in past 6 months	9 (5.2)	5 (3.8)	4 (9.5)	0.38 (0.1-1.48)	0.299	-	-

Variables	Total (%) (n=172)	Adherent patients (n=130)	Non-adherent patients (n=42)	Univariate analysis Odds Ratio (95 % CI)	P value	Multivariable analysis Odds Ratio (95 % CI)	P value
Belief about medicines							
Necessity-concern differential score, median (IQR)	2.0 (1.4-2.8)	2.2 (1.4-2.8)	1.6 (1.2-2.1)	-	0.001	1.1 (0.5-2.3)	0.869
Necessity score, median (IQR)	2.27 (1.7-2.6)	2.2 (1.7-2.5)	2.4 (2.2-2.8)	-	0.001	-	-
Concern score, median (IQR)	4.38 (3.9-4.5)	4.5 (4-4.5)	4.1 (3.8-4.5)	-	0.014	-	-
Social support							
Satisfaction with the support, median (IQR)	3 (2-4)	4 (3-4)	2.5 (2-4)	-	0.005	1.2 (0.7-1.8)	0.525
Extent of support from friends and family, median (IQR)	4 (2-4)	4 (3-4)	2.5 (2-4)	-	0.023	-	-
Using reminder devices	76 (44.2)	73 (56.2)	3 (7.1)	16.65 (4.89-56.64)	<0.001	9.1 (2.0-41.6)	0.004
Healthcare relationship trust score, median (IQR)	3.4 (2.7-3.7)	3.6 (2.8-3.7)	3 (2.5-3.4)	-	<0.001	1.5 (0.8-3.0)	0.231
Waiting time in clinic, median min (IQR)	60 (30-180)	60 (30-120)	180 (120-305)	-	<0.001	-	-

All participants were taking a regimen containing three drugs, composed of two nucleoside reverse transcriptase inhibitors (NRTIs) (zidovudine or tenovofir plus lamivudine) and a NNRTI (nevirapine or efavirenz). Ninety-five (45.9 %) participants took their antiretroviral medication once a day and the remaining took it twice daily. The baseline characteristics of study participants who completed the study are as shown (**Table 4** and **Table 5**).

4.4.2. Patterns of adherence over time

The proportion of non-adherent patients increased over the study period by 4.1 % and 18.4 % from month 3 to 12 for ACTG self-reported and VAS assessments, respectively (**Figure 4**). One hundred and thirty patients (75.6 %) reported optimal ACTG self-reported medication adherence at 12 months and the remaining 42 (24.4 %) patients were considered non-adherent. Identifying the predictors of long-term adherence is important to improve the treatment outcomes of chronic diseases, including HIV/AIDS. Hence, the twelve-month adherence measurements were used in the analysis. The closest measured value of the variables to the 12-month time period was used in the analysis. For instance, stigma was measured at month 2 and month 9 throughout the study period; in this study the 9 month stigma value was used. The decline in mean VAS adherence was statistically significantly over the study period ($p \leq 0.05$). It was significantly different between months 3 and 9 ($p= 0.006$), months 3 and 12 ($p < 0.001$), and months 9 and 12 ($p= 0.034$). Correlations between self-reported ACTG and VAS adherence varied from 0.26 to 0.59 ($P \leq 0.001$) at different points in time.

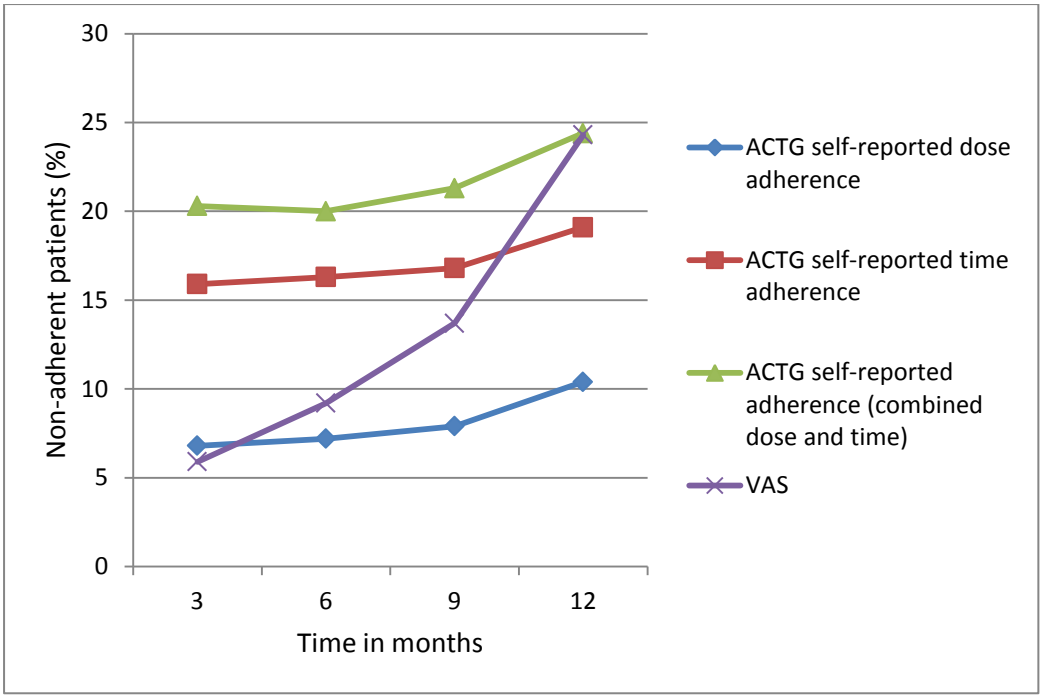


Figure 4. Percentage of non-adherent patients over time by multiple measures.

4.4.3. Treatment outcomes

The median increases in CD4 count, BMI, and weight among adherent and non-adherent patients using multiple adherence measures are shown in Table 6. Among all patients, CD4 count increased from baseline by a median of 146 cells/μL at month 12. The CD4 count increase was significantly higher in the adherent patients compared to non-adherent patients using ACTG self-reported adherence at 12 months (159 cells/μL [IQR, 72-324 cells/μL] vs. 132 cells/μL [IQR, 43-190 cells/μL]; p = 0.026, determined by Mann-Whitney U test). Adherent patients using VAS had a trend towards greater CD4 count gain at 12 months (p=0.056). However, there were no statistically significant differences in CD4 count gain between adherent and non-adherent patients at 12 months using pharmacy record and pill count measures. Stock-outs of a particular regimen which was common in the setting decreased the accuracy of pharmacy record

and pill count adherence measures. Thus, it was decided to focus on the determinants of ACTG self-reported adherence.

Among all participants, weight and BMI increased from the baseline by a median of 3kg and 1.1kg/m2 at month 12. No significant differences in weight and BMI gain were detected between adherent and non-adherent patients using the multiple adherence measures.

4.4.4. Predictors of adherence: univariate analyses

Gender, age, marital status, religion, and living with a child, being alcoholic and chewing khat were not associated with adherence. Factors positively associated with ACTG self-reported adherence were higher educational attainment (secondary school and above), higher scores in HIV treatment knowledge, use of reminders devices (e.g., mobile phone or clock alarms), social support, higher necessity-concerns differential (NCD) scores, higher trust in their HIV care provider, shorter waiting time in the hospitals, and lower depressive symptoms. Factors negatively associated with adherence were higher scores in overall Berger stigma and its subscales, personalized stigma, negative self-image, and public attitudes, and higher HIV symptoms and ADRs (**Table 4** and **Table 5**).

4.4.5. Factors associated with adherence: multivariate analysis

In the multivariate analyses, a higher baseline BMI (OR, 1.2; 95 % CI 1.0, 1.4), and use of reminder devices (OR, 9.1; 95 % CI 2.0, 41.6) remained positively associated with adherence (Table 7), while a higher HIV symptom and ADR distress score was an independent negative predictor of adherence (OR, 0.90; 95% CI 0.9, 1.0).

Table 6. Adherence to ART and clinical outcome.

Endpoint-median (IQR)	Total (n=172)	ACTG self-reported		P value
		Adherent (n=130)	Non-adherent (n=42)	
Change in CD4 count (cells/μL))	146 (62, 279)	159 (72, 324)	132 (43, 190)	0.026
Change in BMI (kg/m^2)	1.1 (0.0, 2.4)	1.1 (0.0, 2.4)	1.4 (-0.3, 2.5)	0.948
Change in body weight (kg)	3.0 (0.0, 6.0)	3 (0.0, 6.0)	4 (-0.8, 6.0)	0.973
		VAS		
		Adherent (n=130)	Non-adherent (n=41)	
Change in CD4 count (cells/μL)	146 (62, 279)	159 (69, 288)	103 (61, 172)	0.056
Change in BMI (kg/m^2)	1.1 (0.0, 2.4)	1.1 (0.0, 2.4)	1.2 (0.0, 2.5)	0.772
Change in body weight (kg)	3.0 (0.0, 6.0)	3.0 (0.0, 6.0)	3.0 (0.0, 6.0)	0.824
		MPR		
		Adherent (n=153)	Non-adherent (n=19)	
Change in CD4 count (cells/μL)	146 (62, 279)	140 (65, 274)	156 (81, 250)	0.749
Change in BMI (kg/m^2)	1.1 (0.0, 2.4)	1.1 (0.0, 2.4)	2.0 (-1.5, 2.5)	0.898
Change in body weight (kg)	3.0 (0.0, 6.0)	3.0 (0.0, 6.0)	5.0 (-4.0, 9.0)	0.927
		Pill count		
		Adherent (n=161)	Non-adherent (n=9)	
Change in CD4 count (cells/μL)	146 (62, 279)	140 (62, 274)	207 (136, 280)	0.485
Change in BMI (kg/m^2)	1.1 (0.0, 2.4)	1.1 (0.0, 2.4)	2.5 (0.5, 3.0)	0.432
Change in body weight (kg)	3.0 (0.0, 6.0)	3.0 (0.0, 6.0)	5.0 (-1.0, 9.0)	0.532

Table 7. Factors included in final logistic regression model.

Variable	Multivariable analysis	
	Odds Ratio (95 % CI)	P value
Education level (Literate)	2.3 (0.8-6.5)	0.127
Full time or par-time employed	0.9 (0.3-2.5)	0.884
Baseline body-mass index, kg/m^2	1.2 (1.0-1.4)	0.048
Nevirapine based	1.4 (0.5-3.7)	0.536
HIV treatment knowledge score (0 to 21)	1.0 (0.8-1.3)	0.927
Depression score ≥ 3	0.9 (0.2-4.9)	0.906
Berger Stigma score	0.9 (0.3-3.0)	0.896
Necessity-concern differential score	1.1 (0.5-2.3)	0.869
HIV symptoms and ADRs distress score	0.9 (0.9-1.0)	0.045
Healthcare relationship trust score	1.5 (0.8-3.0)	0.231
Satisfaction with the support	1.2 (0.7-1.8)	0.525
Using reminder devices	9.1 (2.0-41.6)	0.004

4.5. Discussion

This is the first prospective study to assess the association between a range of variables, including socio-economic, psychological, and disease/regimen-related factors, and self-reported ACTG adherence in adult patients who were initiated on ART in Ethiopia. This long-term study permitted us to reaffirm the dynamic nature of adherence behaviour. The proportions of non-adherent patients increased over time as reported previously by Lazo et al. [231], and at the end of the study period almost one quarter of patients (24.4 %) were found to be non-adherent. VAS adherence measure better identified non-adherent patients in this study; thus clinicians and researchers in resource-limited settings might choice VAS over other measures for this advantage. ACTG self-reported

adherence predicted CD4 count gain and was independently associated with higher BMI, lower HIV symptom and ADR distress, and use of reminder devices in this study. We believe that these findings have important implications for improving services and interventions for patients taking ART in Ethiopia following the remarkable scale-up over the past decade.

Findings from previous studies are inconsistent on the association between socio-demographic characteristics and adherence [223, 232-234]. Most of the socio-demographic characteristics evaluated in this study did not predict optimal adherence. The lack of associations between socio-demographic characteristics and adherence in this study sample is not surprising given that treatment is provided free of charge and physical access to healthcare has been improving in Ethiopia.

In this study, we also demonstrated that lower HIV symptom and ADR distress scores were independently associated with adherence to ART. To our knowledge, this is the first study to demonstrate this relationship. Symptoms attributed to HIV infection and/or ADRs of ART are an important source of distress [235]. Reynolds et al. [236] reported that HIV symptom distress correlated with non-adherence to non-antiretrovirals in patients naïve to ART. Previous studies have mainly focused on non-specific perceived distress in HIV patients and reported inconsistent findings on the role of distress on treatment outcomes [90, 237]. Some studies have demonstrated that distress predicted non-adherence to ART [237, 238], CD4 count decline [239], and virologic failure [240]. Distress precipitates negative health behaviour (e.g., forgetting to take pills, drinking alcohol more than usual, etc.) [239] that may impair patients from achieving optimal adherence to ART.

All patients in this study were ART naïve; HIV symptoms and ADRs are more frequent in this patient group compared to ART experienced patients [241]. It is therefore not unexpected that distress associated with HIV symptoms and medication ADRs predicted non-adherence in this study. Given our findings regarding the association between adherence and increase in CD4 count, distress associated with HIV symptoms and ADRs has important implications for treatment outcomes. Thus routine monitoring for HIV symptoms and ADRs are needed in Ethiopian patients initiated on ART to improve adherence and thereby patient outcomes.

Use of medication reminder devices was positively associated with adherence to ART in this study. Mobile phone ownership has grown dramatically in sub-Saharan Africa, including Ethiopia [242]. In our study, almost four out of five patients possessed a mobile phone of whom more than 64% were able to send and receive a text-message reminder. A randomised control trial in Kenya [155, 156] reported short message services improved adherence to ART. Other reminder devices such as clock and watch alarms could also be a tool to help patients taking long term medication such as ART in resource-limited settings. Clinics should propose programmes that teach patients how to use mobile and other reminder devices to promote adherence to ART and thereby treatment outcomes.

Strengths of this study include the prospective design with previously validated questionnaires that enabled us to determine factors associated with long-term non-adherence to ART, and the fact that a wide range of factors were evaluated. Its prospective nature also allowed assessment of changing adherence levels over time. These data do have several limitations, however. Firstly, we used self-reported adherence measures for our data analyses although objective measures, such as pill

count and dispensing records, are believed to be more precise in comparative studies [243-245]. Self-reported measures are subject to social desirability and recall biases and thus may overestimate adherence. The ACTG self-reported adherence method is convenient and inexpensive and has been the most commonly used method in both resource-poor and resource-rich clinical settings [93, 95, 231, 246]. This method was better in predicting an increase in CD4 count within 12 months than other measures in this study. The precision of self-reported adherence in this study may have improved over other studies as the result of the amalgamation of time and dose adherence, and the relatively short time frame (in the last 7 days) to reduce the potential recall bias. The wording in the instrument was non-judgmental and research pharmacists who were not directly involved in patient care administered the instrument. Secondly, the impact of adherence on treatment outcome in this study was monitored using change in CD4 count, which tends to occur later and is, consequently, less visible than the impact on HIV viral load [247]. However, the Home-Based AIDS Care Project (HBAC) [248] in Uganda reported that clinical monitoring with quarterly CD4 count was more cost-effective, with no significant difference in rates of new AIDS-defining events or deaths, compared with clinical monitoring with quarterly CD4 count and HIV viral load monitoring. Clinical monitoring with biannual CD4 counts is used to routinely monitor treatment response for patients taking ART in Ethiopia.

4.6. Conclusion

Improvement of treatment and care access for patients with HIV/AIDS has been the key clinical achievement in Ethiopia over the past decade. This study found that higher BMI, lower HIV symptom and ADRs distress scores, and use of reminder devices were independent predictors of self-reported adherence. Implementation of measures to

consistently monitor HIV symptoms and ADRs distress and malnutrition, and to promote the use of reminder devices may improve adherence and treatment outcomes in patients initiated on ART.

CHAPTER FIVE

5. ADVERSE DRUG REACTIONS AND CLINICAL OUTCOMES IN PATIENTS INITIATED ON ANTIRETROVIRAL THERAPY: A PROSPECTIVE COHORT STUDY FROM ETHIOPIA

5.1. Abstract

Background The use of antiretroviral therapy (ART) has been scaled-up for HIV/AIDS in Ethiopia over the past decade. Adverse drug reactions (ADRs) associated with ART pose a unique challenge in the treatment of the infection in this resource-limited setting.

Objectives The aim of this study was to examine the incidence and nature of ADRs, identify the risk factors associated with the development of ADRs, and assess their impact on treatment outcomes.

Methods A prospective cohort study was conducted in adult patients (≥18 years) with HIV/AIDS commenced on ART. All ADRs in the first 12 months of therapy were recorded, and the severity, causality, and preventability assessed. The impact of severe ADRs on self-reported adherence, immunological, and body mass index (BMI) outcomes were assessed.

Results Of the 211 patients included in the analysis, 181 (85.7%) experienced at least one ADR and 66 (31.3%) experienced at least one severe ADR within 12 months of commencing ART (incidence rates for any ADR and severe ADR of 14.8 and 3.2 per 100 person-months, respectively). Logistic regression analysis indicated that taking zidovudine-containing regimens [Odds Ratio (OR)=4.2, 95% CI (2.1-8.4)] or being unemployed [OR=2.2, 95% CI (1.1-4.3)] were independent predictors of experiencing

severe ADRs. Patients who experienced a severe ADR were less likely [OR=0.4, 95% CI (0.2-0.9)] to be ≥90% adherent to ART. The mean gain in BMI was significantly lower in patients with severe ADRs after 3 months or 12 months of therapy.

Conclusions ADRs were common within the first three months in patients initiated on ART. Severe ADRs were negatively associated with self-reported adherence and gain in BMI. Measures need to be implemented to routinely monitor for severe ADRs to improve ART adherence and treatment outcomes.

Key Points

- One-third of patients initiated on ART experienced severe ADRs over a one-year period.
- Most severe ADRs were reported within the first three months and found to have negative impact on treatment outcomes in patients initiated on ART.
- Almost half of the severe ADRs related with ART were found to be preventable, highlighting the importance of improving antiretroviral prescribing and monitoring practices.

5.2. Introduction

At the end of 2012, 35.3 million people were living with Human Immunodeficiency Virus (HIV) and 9.7 million people (61% of eligible patients) were on Antiretroviral Therapy (ART) worldwide [249]. ART has decreased mortality and morbidity, and improved the quality of life of patients with HIV [216]. However, ART can also cause undesirable adverse drug reactions (ADRs) that are among the most important reasons for medication non-adherence, treatment switch or discontinuation, and virologic failure [62, 250-252].

A free ART programme was introduced in Ethiopia in 2005 [184, 188]. Over the past 10 years, decentralisation and scale-up of the programme has occurred [249] and 743 free ART centres have been established across the country. A total of 249,174 adult patients (86% of eligible patients) were on ART as of 2011 [183, 249].

Detection of ADRs in Ethiopian ART clinics provides an important assessment of the burden of antiretroviral-associated morbidity in the HIV care programme. To our knowledge, only a few retrospective studies have attempted to identify the type and frequency of ADRs in Ethiopian adult patients receiving ART [253, 254], and given the poor documentation of ADRs in patients' medical charts, ADRs are underreported. In addition, the impact of ADRs on treatment outcomes (body mass index (BMI), and CD4 count) has not been evaluated. In resource-limited settings, BMI and CD4 count are useful surrogate markers of treatment outcomes [255].

The aim of this study was to prospectively examine the incidence and nature of ADRs, identify the risk factors associated with the development of ADRs, and assess their impact on treatment outcomes in Ethiopian patients with HIV/Acquired Immune Deficiency Syndrome (AIDS) who commenced ART.

5.3. Methods

This was a prospective cohort study, in which adult patients (≥18 years) with HIV/AIDS who commenced on ART were followed from the time of ART commencement (month (M)=00) to 12 months (M=12) of therapy. The study was conducted from 18 December 2012 to 18 May 2014 at Felege-Hiwot and Gondar University Hospitals. Nurses and research pharmacists recruited patients from the ART clinics. All participants provided written informed consent for their involvement in the study. Details of the study setting have previously been described [225].

Adult HIV-infected patients were eligible to start ART when their CD4 count was less than or equal to 350 cells/μL regardless of the clinical symptoms, or with any symptoms indicating a World Health Organization (WHO) clinical stage of 3 or 4, irrespective of CD4 count. ART initiation was informed by the Ethiopian '*Guidelines for management of opportunistic infections and antiretroviral treatment in adolescents and adults in Ethiopia 2008*' and the WHO '*Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach 2010 revision*' [256, 257]. ART-initiated patients had an appointment every month for the first 6 months and every 3 months thereafter in ART clinics. A research pharmacist was assigned to each hospital's ART clinic to assess ADRs throughout the study period. Patients were also asked to report any potential ADRs. ADRs that continued for subsequent appointments without recovery were reported once. The research pharmacists, who were experienced in clinical care in public health facilities, interviewed patients, caregivers and physicians, reviewed patients' medical records and documented detailed information for each of the potential ADRs that patients experienced. An ADR was defined according to the WHO definition as "a response to a drug that is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease, or for modification of physiological function" [258]. ADRs were evaluated based on the clinical signs and symptoms, and laboratory tests. The severity, causality, and preventability of ADRs were assessed using the Division of AIDS Adverse Events (DAIDS AE) grading table [259], Naranjo's probability scale [209], and the Schumock and Thornton criteria [211], respectively. The management and outcomes of ADRs were also recorded. These data were independently reviewed by a second research pharmacist, blinded to the first pharmacist's assessment, to ensure their accuracy and validity.

When there was a disagreement in the assessment of an ADR, the pharmacists resolved their disagreement through discussion until consensus was reached.

Socio-demographic and clinical information, such as age, gender, level of education, employment status, comorbidities, WHO stage of HIV/AIDS, weight and height, and laboratory test results performed in the hospitals, including CD4 count, haematocrit, white blood cell (WBC) count, absolute neutrophil count, platelet count, liver function and renal function, were recorded from each patient's medical record. Similarly, details of the ART regimen and other concomitant medications were also recorded. An increase in CD4 counts of more than 50cells/μL from the baseline was defined as immunological response [260].

Dose adherence to ART was measured using a modified AIDS Clinical Trial Group (ACTG) self-reported adherence questionnaire that asks patients how many doses they missed in last 7 days. Similarly, time adherence was measured using the four-item Likert-type modified ACTG questionnaire [90]. Details of multiple medication adherence measures have previously been reported [225]. Responses to the two questions were translated into dose and time adherence scores ranging from 0 to 100% over the 7-day period, and the average of the two measures was taken as a combined indicator of dose and time adherence.

The frequency of ADRs was described using descriptive statistics. Characteristics of patients who experienced ADRs and those who did not were compared using Pearson's χ^2 tests for gender, age, level of education, employment status, immunological response (CD4 count), WHO HIV stage, history of drug allergy, type of ART regimen, comorbidities, concomitant medications, and self-reported adherence. Logistic regression analysis was undertaken to determine the independent predictors of severe

ADRs (grades 3 and 4 using the DAIDS AE grading table), cutaneous reactions, gastrointestinal complaints, and neuropsychiatric reactions where univariate analyses suggested association with multiple risk factors. Factors with a p value of ≤0.2 in univariate analysis were entered into the logistic regression model after checking multicollinearity. Results are presented in terms of odds ratio (OR) for each risk factor followed by a 95% confidence interval (CI). Mean changes in body mass index after 3 months and 12 months of ART were compared between patient groups with independent samples t tests. Data were analysed using SPSS version 21 (IBM Corp., New York, USA). A value of $p < 0.05$ was considered statistically significant.

Ethical approvals were received from the Tasmanian Health and Medical Human Research Ethics Committee (H0012722) and Bahir-Dar University's ethics committee (RCS/567/2004).

5.4. Results

During the 4-month recruitment period (18 December 2012 to 17 March 2013), 337 adults (≥18 years; 191 females and 146 males) commenced ART at the two sites. Of these, 246 patients (143 females and 103 males) enrolled in this study. The ninety-one patients did not take apart in this study because of our exclusion criteria (patients who were initiated on ART in the study clinics but whose follow-up was in outlying areas were excluded) and not consenting to participate in this study. There were no significant differences in the WHO stage of HIV/AIDS, gender, age, CD4 count and weight between subjects who did and did not participate in the study. Thirty-five patients who did not complete at least 3 months' follow-up (9 lost to follow-up, 11 withdrawn, 10 died, and 5 transferred to other clinics) were excluded from this analysis. As shown in Table 8, of the 211 patients included in study, 60% were female.

Their median baseline CD4 count and BMI were 183 cells/μL and 19.4 kg/m^2, respectively.

All patients were receiving an ART regimen containing three drugs - two nucleoside reverse transcriptase inhibitors (NRTIs) (zidovudine plus lamivudine, or tenofovir plus lamivudine) plus one non-nucleoside reverse transcriptase inhibitor (NNRTI) (efavirenz or nevirapine) at baseline. One hundred and twelve (53%) patients were taking a zidovudine plus lamivudine-containing regimen, and 109 (52%) patients were taking an efavirenz-containing regimen. Self-reported dose adherence in the study sample was 97.7% at 3 months. The rate of adherence considering the combined (dose and time) indicator was 93.8% at 3 months.

Table 8. Baseline patient characteristics (n=211).

Characteristic	Number (%)	Median	IQR
Women	127 (60.2)		
Age		32	27-38
Education level			
Illiterate	115 (54.5)		
Literate	96 (45.5)		
Employment			
Unemployed	116 (55)		
Employed	95 (45)		
BMI (kg/m^2)		19.4	18.0-21.9
History of drug allergy	16 (7.6)		
Baseline WHO staging*			
Stage I&II	97 (46.0)		
Stage III&IV	105 (49.8)		
ART regimen			
Zidovudine based	112 (53.1)		
Tenofovir based	97 (46.0)		
Stavudine based	2 (0.9)		
Efavirenz based	109 (51.7)		
Nevirapine based	102 (48.3)		
Baseline CD4 (cells/μL)**		183	94-252

IQR = interquartile range, BMI = body mass index, ART = antiretroviral therapy

*Total does not add up to 211 due to missing data.

**1 missing value.

Table 9. Frequency of potential adverse drug reactions of antiretroviral therapy.

Specific ADR by organ	Number of cases (%) (n=211)	TDF+3TC+EFV (n=87)	TDF+3TC +NVP (n=10)	ZDV+3TC+EFV (n=22)	ZDV+3TC+NVP (n=90)
Gastrointestinal	115 (54.5)	28 (32.1)	6 (60.0)	12 (54.5)	66 (73.3)
Nausea	60 (28.4)	11 (12.6)	3 (30)	8 (36.4)	38 (42.2)
Vomiting	30 (14.2)	8 (9.2)	3 (30)	2 (9.1)	16 (17.7)
Anorexia	4 (1.9)	1 (1.1)	-	1 (4.5)	3 (3.3)
Diarrhoea	3 (1.4)	1 (1.1)	-	-	2 (2.2)
Gastric discomfort	12 (5.7)	4 (4.6)	-	1 (4.5)	5 (5.5)
Gastritis	6 (2.8)	3 (3.4)	-	-	2 (2.2)
Neuropsychiatric	113 (53.5)	76 (87.3)	2 (20)	20 (90.9)	14 (15.5)
Headache	37 (17.5)	19 (21.8)	2 (20)	4 (18.2)	10 (11.1)
Nightmare	17 (8.0)	14 (16.1)	-	3 (13.6)	-
Confusion	9 (4.2)	7 (8.0)	-	2 (9.1)	-
Somnolence	1 (0.5)	-	-	-	1 (1.1)
Insomnia	10 (4.7)	7 (8.0)	-	1 (4.5)	2 (2.2)
Vertigo	23 (10.9)	16 (18.4)	-	7 (31.8)	-
Anxiety	1 (0.5)	-	-	1 (4.5)	-
Tingling	1 (0.5)	1 (1.1)	-	-	-
Dizziness	5 (2.4)	4 (4.6)	-	-	1 (1.1)
Numbness	1 (0.5)	1 (1.1)	-	-	-
Hearing loss	1 (0.5)	-	-	1 (4.5)	-
Psychosis	1 (0.5)	1 (1.1)	-	-	-
Hallucination	2 (0.9)	1 (1.1)	-	1 (4.5)	-
Depression	2 (0.9)	2 (2.3)	-	-	-

Specific ADR by organ	Number of cases (%) (n=211)	TDF+3TC+EFV (n=87)	TDF+3TC +NVP (n=10)	ZDV+3TC+EFV (n=22)	ZDV+3TC+NVP (n=90)
Lethargy	1 (0.5)	1 (1.1)	-	-	-
Trouble remembering	1 (0.5)	1 (1.1)	-	-	-
Agitation	1 (0.5)	1 (1.1)	-	-	-
Cutaneous reaction	66 (31.3)	24 (27.6)	4 (40)	9 (40.9)	28 (31.1)
Skin rash	39 (18.5)	17 (19.5)	2 (20)	6 (27.3)	14 (15.5)
Allergic dermatitis	5 (2.4)	-	-	1 (4.5)	4 (4.4)
Nail pigmentation	3 (1.4)	-	-	-	3 (3.3)
Pruritus	15 (7.1)	7 (8.0)	2 (20)	3 (13.6)	3 (3.3)
Erythema multiforme	1 (0.5)	-	-	-	1 (1.1)
Erythema	1 (0.5)	-	-	-	1 (1.1)
Hepatotoxicity	2 (0.9)	1 (1.1)	1 (10)	-	-
Nephrotoxicity	2 (0.9)	2 (2.3)	-	-	-
Systemic signs/symptoms	23 (10.9)	4 (4.6)	-	3 (13.6)	15 (16.6)
Fever	10 (4.7)	3 (3.4)	-	1 (4.5)	6 (6.6)
Fatigue	13 (6.2)	1 (1.1)	-	2 (9)	9 (10)
Musculoskeletal	12 (5.7)	3 (3.4)	1 (10)	2 (4.5)	6 (6.6)
Arthralgia	7 (3.3)	2 (2.3)	-	2 (4.5)	3 (3.3)
Muscle pain	5 (2.4)	1 (1.1)	1 (10)	-	3 (3.3)
Haematological	16 (7.6)	4 (4.7)	-	5 (22.7)	7 (7.7)
Anaemia	13 (6.2)	1 (1.1)	-	5 (22.7)	7 (7.7)
Thrombocytopaenia	3 (1.4)	3 (3.4)	-	-	-

TDF=tenofovir, 3TC=lamivudine, ZDV=zidovudine, EFV=efavirenz, NVP=nevirapine.

Throughout the study period 370 ADRs were identified Table 9. Twenty-one ADRs were excluded from analysis as their causal relationship with ART regimens was rated as doubtful according to Naranjo's scale; 66.5% and 31.8% of ADRs had a possible and probable causal relationship with the ART regimen, respectively, as shown in Table 10. Most ADRs were rated as grade 1 (52.7%) and grade 2 (25.2%) using the DAIDS AE grading table; 22.1% were graded as severe (grades 3 and 4).

ADRs were common - 181 (85.7%) patients experienced at least one ADR, and 66 (31.3%) experienced severe (grade 3 or 4) ADRs. The prevalence of ADRs was similar in females (86.6%) and males (84.5%). Ninety-seven (45%) patients reported more than one ADR; 78 (37%) patients had two or three ADRs, and 19 (9%) patients had four or five ADRs.

The onset and distribution of ADRs within the study period are shown in **Figure 5**. Ninety percent of ADRs (314) were reported within the first three months of ART. Seventy-seven severe ADRs were reported throughout the study period and 69 (89.6%) of them occurred within the first three months. The total duration of follow-up time was 2362 person-months, yielding an incidence rate of patients experiencing ADRs as 14.7 per 100 person-months. The corresponding incidence rate for severe ADRs was 3.2 per 100 person-months.

Using univariate analyses, unemployment ($p=0.05$), zidovudine-based regimens ($p<0.001$) and nevirapine-based regimens ($p<0.001$) were associated with the occurrence of severe ADRs. Logistic regression analysis indicated that taking zidovudine-containing regimens [OR=4.2, 95% CI (2.1-8.4)] or being unemployed [OR=2.2, 95% CI (1.1-4.3)] were independent predictors of experiencing severe ADRs Table 11. The most common classes of ADRs were gastrointestinal complaints (54.5%)

followed by neuropsychiatric disorders (32.4%) and skin reactions (31.3%). Nausea (28.4%) followed by skin rash (18.5%) and headache (17.5%) were the most frequently reported specific ADRs. Regimens containing zidovudine were significantly associated with development of gastrointestinal ADRs (p=0.001) and anaemia (P<0.05). There was a significant association between regimens containing efavirenz or zidovudine and neuropsychiatric reactions (p<0.001). Female gender (p<0.05) and a previous history of allergy to any medications (p<0.05) were risk factors for cutaneous reactions. History of allergy (OR=5.3, 95% CI (1.7-16.3)] was more strongly associated with the occurrence of skin reactions in a logistic regression model than was female gender [OR=2.0, 95% CI (1.1-3.9)].

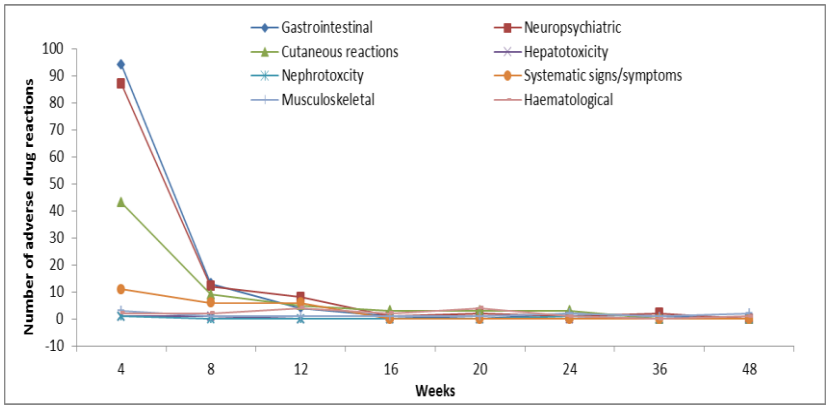


Figure 5. Distribution and time of onset of adverse drug reactions.

Fifty-seven (16.3%), and 38 (47.5%) ADRs and severe ADRs, respectively, were preventable based on the Schumock and Thornton criteria. Symptomatic treatments and substitution of the offending antiretroviral agents were reported for 41 (11.7%) and 22 (6.3%) ADRs, respectively. Alteration of the ART regimen occurred in 28 (13.3%) patients throughout the study period and, of these, 22 (78%) were due to the development of severe ADRs. Twenty (35%) preventable severe ADRs were gastrointestinal complaints associated with zidovudine-containing regimens. Of them

only three patients received symptomatic treatment. Nineteen (33%) preventable ADRs were due to inadequate laboratory monitoring of drug toxicities. Of them, 12 (63%) ADRs were anaemia associated with zidovudine-containing regimens. Skin reactions were third important class of preventable ADRs, behind gastrointestinal complaints and anaemia in this study. Among thirty-four female patients who had a baseline CD4 count more than 250 cells/μL, twenty-one (60%) were inappropriately taking a nevirapine-based regimen according to Ethiopian guidelines [256]. Of these, seven patients developed skin reactions, three of which were severe.

Table 10. Assessment and management of adverse drug reactions.

		Adverse drug reactions								
		Gastrointestinal	Neuropsychiatric	Cutaneous reaction	Hepatotoxicity	Nephrotoxicity	Systemic signs/symptoms	Musculoskeletal	Haematological	Total
Number cases		115	113	66	2	2	23	12	16	349
Causality	Definite	-	-	-	-	2 (100)	-	-	4 (25)	6 (1.7)
	Probable	32 (27.8)	4 (3.5)	52 (78.7)	2 (100)	-	3 (13)	6 (50)	12 (75)	111 (31.8)
	Possible	83 (72.2)	109 (96.5)	14 (21.2)	-	-	20 (86.9)	6 (50)	-	232 (66.5)
Severity	Grade 1	46 (40)	83 (73.4)	32 (48.5)	-	-	12 (52.2)	5 (4.2)	6 (37.5)	184 (52.7)
	Grade 2	21 (18.3)	25 (22.1)	25 (37.8)	1 (50)	-	7 (30.4)	6 (50)	3 (18.7)	88 (25.2)
	Grade 3	45 (39.1)	5 (4.4)	6 (9.1)	-	-	4 (17.4)	-	2 (12.5)	62 (17.7)
	Grade 4	3 (2.6)	-	3 (4.5)	1 (50)	2 (100)	-	1 (8.3)	5 (31.3)	15 (4.3)
Preventability	Yes	24 (20.9)	2 (1.7)	8 (12.1)	2 (100)	2 (100)	3 (13.0)	2 (16.7)	16 (100)	57 (16.3)
	No	91 (79.1)	111 (98.3)	58 (87.9)	-	-	20 (87)	10 (83.3)	-	292 (83.7)
Intervention*	Drug withdrawal	3 (2.6)	1 (0.9)	6 (9.1)	1 (50)	2 (100)	1 (4.3)	-	8 (50)	22 (6.3)
	Symptomatic treatment Yes	12 (10.4)	6 (5.3)	12 (18.2)	-	-	5 (21.7)	4 (33.3)	2 (12.5)	41 (11.7)
	No	100 (86.9)	106 (93.8)	48 (72.7)	1 (50)	-	17 (73.9)	8 (66.6)	1 (6.25)	281 (80.5)

* Intervention data for 5 ADRs were not available

The potential influence of severe ADRs on treatment outcomes was evaluated with consideration of the combined self-reported 7-day recall dose and time adherence to ART and increased absolute CD4 count and BMI. Patients who experienced a severe ADR within the first three months were significantly less likely [OR=0.4, 95% CI (0.2-0.9), $p<0.05$] to be adherent when using combined dose and time (>=90%) adherence to ART within the first three months of treatment. However, after 3 months of ART, there was no significant association between severe ADRs and adherence.

The mean BMI at baseline was 20.0±3.1 kg/m^2 in those who experienced severe ADRs, and 20.0±3.4 kg/m^2 in those who did not experience severe ADRs. There were significant differences between these patient groups in terms of mean change in BMI at 3 and 12 months of therapy ($p\leq0.05$). Among those who experienced severe ADRs, the mean BMI increased by 0.6±2.7 kg/m^2 over 12 months, while the mean BMI rose by 1.5±2.2 kg/m^2 in patients who did not experience severe ADRs over the same period. However, there were no significant differences in immunological response (CD4 count) in these patient groups at different time points Table 12.

Table 11. Risk factors for adverse drug reactions.

Adverse drug reactions	Variables associated with ADR	χ^2 test		Logistic regression	
		OR (95% CI)	P value	OR (95% CI)	P value
Severe ADR	Zidovudine based regimens	3.5 (2.0-6.9)	<0.001	4.2 (2.1-8.4)	<0.001
	Nevirapine based regimens	3.5 (1.9-6.4)	<0.001	-	-
	Unemployed	1.9 (1.0-3.5)	0.050	2.2 (1.1-4.3)	0.024
	WHO stage III &IV	0.6 (0.3-1.1)	0.123	0.6 (0.3-1.2)	0.163
	Eating once per day	1.6 (0.8-3.3)	0.194	1.6 (0.7-3.5)	0.266
Gastrointestinal	Zidovudine based regimens	2.6 (1.5-4.6)	0.001	2.5 (1.4-4.5)	0.002
	Education-no	0.7 (0.4-1.1)	0.153	0.7 (0.4-1.3)	0.316
Neuropsychiatric	Efavirenz based regimens	7.24 (3.8-13.7)	<0.001	8.0 (4.0-15.9)	<0.001
	Tenofovir based regimens	3.7 (2-5)	<0.001	-	-
	Female gender	1.5 (0.9-2.7)	0.190	0.7 (0.4-1.5)	0.394
	BMI ≤19.5 kg/m^2	1.5 (0.8-2.5)	0.220	1.3 (0.6-2.5)	0.535
	Age ≤ 30 years	1.6 (0.9-2.7)	0.124	1.5 (0.8-3.0)	0.237
	Eating once a day	1.70 (0.8-3.5)	0.200	1.8 (0.8-4.1)	0.165
Skin reactions	Female gender	2.0 (1.1-3.8)	0.0413	2.0 (1.1-3.9)	0.034
	History of drug allergy	5.3 (1.7-16.2)	0.003	5.3 (1.7-16.3)	0.004
Haematological	Zidovudine based regimens	4.0 (1.1-14.5)	0.050	-	-

Table 12. Clinical outcomes and adverse drug reactions.

Adherence or Gain in BMI or CD4 cells	Severe ADR	No Severe ADR	χ^2 test OR (95%CI)	P value
Adherent (>=90%) patients at month 3	43 (27.2)	115 (72.8)	0.4 (0.2-0.9)	0.046
Adherent (>=90%) patients at month 6	49 (31.6)	106 (80.9)	1.1 (0.5-2.6)	0.882
Adherent (>=90%) patients at month 9	45 (28.8)	111 (84.8)	0.7 (0.3-1.5)	0.448
Adherent (>=90%) patients at month 12	39 (27.9)	101 (72.1)	0.7 (0.3-1.4)	0.385
Gain CD4 ≥+50 cells/μL within 6 months	38 (31.4)	83 (68.6)	1.0 (0.4-2.4)	1.000
Gain CD4 ≥+50 cells/μL within 12 months	41 (31.8)	88 (68.2)	1.2 (0.5-3.0)	0.826
			t test	P value
BMI (kg/m^2) change within 3 months	+0.29±1.52	+0.88±1.59		0.017
BMI (kg/m^2) change within 12 months	+0.61 ± 2.73	+1.50 ± 2.22		0.027

5.5. Discussion

This is the first prospective cohort study assessing the incidence, type, severity, causality, preventability, predictors, and treatment outcomes of ADRs in patients who were initiated on ART in Ethiopia. The study revealed that the incidence rate of severe ADRs over one year was 3.2 per 100 person-months, with 89.6% of severe ADRs reported within the first three months of ART. Most of the severe ADRs were gastrointestinal complaints, haematological, and skin reactions. Taking zidovudine-based regimens and being unemployed were shown to be independent risk factors for severe ADRs. The findings of this study regarding patient groups at risk of ADRs are especially important in that they suggest a number of practical interventions that could be readily implemented in clinical practice to minimise patients' risk of developing

ADRs. This would represent a significant advance in HIV/AIDS management in Ethiopia as our study demonstrated that severe ADRs were associated with not only self-reported non-adherence with therapy (the importance of optimal adherence to ART in optimising patient outcomes is well-recognised [261, 262]) but also a poorer patient outcome in terms of gain in BMI.

In the study period, 86% of patients reported at least one ADR and more than one-third experienced a severe ADR. The high prevalence of ADRs in this study might be associated with intensive prospective data collection, which assisted to identify mild ADRs that might be unreported in other studies. Studies that followed a similar methodology in Iranian and Indian patients who commenced ART had also reported a high prevalence of ADRs - 88% and 90%, respectively, over two-year study periods [241, 263].

Zidovudine-containing regimens were a risk factor for gastrointestinal, haematological, and severe ADRs. Other studies had also reported NRTIs as a risk factor for the occurrence of gastrointestinal problems [264]. The overall prevalence of gastrointestinal complaints (54.5%) was lower than reported in a cohort of Iranian patients (67.3%), where 81% of patients were taking a zidovudine-based regimen [241]. However, the prevalence in this sample was higher than reported in Nigerian patients (34%) of whom 57.7% were taking zidovudine-containing regimens [265]. Although most of the gastrointestinal problems were mild and self-limiting, they were typically observed in the first 8 weeks of therapy and therefore had potential to strongly influence patients' perceptions of their treatment. Perhaps because of this, gastrointestinal ADRs are one of the documented reasons for medication non-adherence [266].

The prevalence of anaemia in this study was low (6.2%) and similar to that in studies reported in Nigeria (4%), India (3.1%), and Haiti (4.7%) [267-269]. Given that many patients with HIV/AIDS in Ethiopia have coexisting malnutrition and chronic diseases, and 60% of study participants were female, the relatively low prevalence of anaemia was unexpected. Prospective cohort studies in Iranian and Indian patients reported higher incidences of anaemia (22% and 10.3%, respectively), although more than 94% of patients who developed anaemia in these studies were receiving zidovudine-based ART regimens [241, 263]. One possible explanation for the relatively lower prevalence of anaemia in the current study is the lower rate of use of zidovudine-based regimens compared to these previous studies.

Neuropsychiatric ADRs generally appeared within first few days of treatment and resolved after 4-8 weeks of therapy. However, this short-term ADR may be intolerable and the cause of patient drop out, as reported in our previous study [270], thus patient education and regimen switch may improve adherence to ART and retention in care.

The prevalence of cutaneous reactions reported in this study, 31.3%, was similar to that reported in Nigeria (26.2%) [265], and higher than reported in Côte d'Ivoire (14%) [271] and India (9.2%) [272]. There was no significant difference in rates of skin reactions between nevirapine and efavirenz-containing regimens in this sample, unlike studies reported elsewhere [62, 273]. Female gender and previous history of allergy were implicated as risk factors for experiencing cutaneous reactions in our logistic regression analysis. Hormonal and metabolic factors may play a role in the observed gender disparity in the development of NNRTI-associated rash [274-276]. Our data suggest the need for close monitoring when nevirapine or efavirenz is initiated in patients with these risk factors.

Most severe ADRs were reported within the first three months. Patients who experienced severe ADRs were non-adherent, as reported in other studies [48, 263], and experienced a smaller increase in BMI. Early non-adherence to first-line regimens is associated with emergence of early and late regimen failure [261, 277] and increasing treatment costs [278]. To our knowledge, there have been no previous studies that reported that severe ADRs were associated with a smaller gain in BMI. ADRs such as nausea reduce food intake and subsequently a gain in BMI. In addition, patients who took zidovudine-containing regimens, as reported elsewhere [264], and the unemployed were more likely to develop severe ADRs in this sample. Studies in sub-Saharan patients [279], including our previous study [270], reported that eating insufficient food, which is more likely related with unemployment, exacerbated ADRs with ART. The relationship between severe ADRs and unemployment may be mediated by diagnosis of advanced HIV/AIDS. A previous study has reported that diagnosis of advanced HIV/AIDS, which decreases labour productivity and the chance of employment [280], increased the severity of ADRs with ART [281]. Complexities of ART regimens (e.g. number of doses per day, number of pills per dose) are related with poor adherence in other studies [282]. We found no association between dosing frequency and adherence in our unpublished data.

In this study we found that severe ADRs were more likely to be preventable than less severe ADRs as reported elsewhere [283]. Almost half of the severe ADRs in patients initiated on ART were preventable, which is considerably less than a preventability rate (82.7%) reported in a similar study in India [269]. Medication errors related to preventable ADRs occurred more frequently at the prescribing and monitoring stages of therapy than at the dispensing in this study. Nevirapine was prescribed in more than

60% of female patients who had baseline CD4 count >250 cells/μL, although treatment guidelines recommend the use of abacavir or efavirenz in these patients [256]; this increased these patients' risk for developing skin reactions. Interventions (e.g. dietary modification, patient reassurance) to manage gastrointestinal complaints associated with zidovudine-containing regimens were rarely implemented, which potentially increased the severity of these ADRs. Similarly, inadequate laboratory monitoring for zidovudine-related toxicities may have increased the risk of developing severe anaemia in this study.

Immunologic outcomes throughout the study period were not different in patients with and without severe ADRs. Non-adherence associated with short-term ADRs may not prevent patients making gains in CD4 count. Messou et al. [284] reported that patients who had detectable viral-load achieved comparable CD4 counts at 6 months to those with undetectable viral load. Outcomes of ART in patients who experience short-term severe ADRs may be better monitored using viral-load measurement.

The strengths of our study include the prospective nature, which permitted more precise recording of symptoms and assessment of severity, causality, and preventability of ADRs. To minimise the occurrence of a Hawthorne effect, data were collected through research pharmacists working for our study project only. Staff members working in the ART clinics were neither involved in data collection nor received feedback about the results of the study before its completion.

This study has several limitations. Laboratory ADRs were under-reported in our findings due to a limited number of laboratory tests being performed for monitoring ADRs in these resource-limited hospitals. In addition, there was a lack of continuity with

healthcare providers in ordering the recommended laboratory tests according to treatment guidelines.

The majority of severe ADRs were associated with errors in prescribing and monitoring of regimens that contain zidovudine and/or nevirapine. This study highlights the significance of improving prescribing and monitoring practices in Ethiopian ART clinics to decrease the risk of severe ADRs. Changing the paper based prescribing practice in the ART clinics to a computer based prescribing practice has the potential to decrease errors by providing feedback and suggestions to providers to select the recommended antiretrovirals, and to order laboratory tests for monitoring ADRs in time. Future implementation of the WHO 2013 ART guideline [27], which downgrades zidovudine from a preferred first-line agent, may improve the success of the ART scale-up programme in Ethiopia by reducing the incidence of anaemia and severe ADRs.

5.6. Conclusion

We found that the majority of severe ADRs were reported within the first three months of ART. Taking zidovudine-based regimens and being unemployed were significant risk factors for development of severe ADRs. We observed that severe ADRs were negatively associated with self-reported adherence, and gain in BMI within the first three months. Future studies should focus on prescribing and monitoring of ART, particularly in treatment naïve patients who are vulnerable to severe ADRs, to improve ART adherence and treatment outcomes.

CHAPTER SIX

6. BARRIERS TO AND FACILITATORS OF ADHERENCE TO ANTIRETROVIRAL DRUG THERAPY AND RETENTION IN CARE AMONG ADULT HIV-POSITIVE PATIENTS: A QUALITATIVE STUDY FROM ETHIOPIA

6.1. Abstract

Background: Antiretroviral therapy (ART) has been life saving for hundreds of thousands of Ethiopians. With increased availability of ART in recent years, achievement of optimal adherence and patient retention are becoming the greatest challenges in the management of HIV/AIDS in Ethiopia. However, few studies have explored factors influencing medication adherence to ART and retention in follow-up care among adult Ethiopian HIV-positive patients, especially in the Amhara region of the country, where almost one-third of the country's ART is prescribed. The aim of this qualitative study was to collect such data from patients and healthcare providers in the Amhara region of Ethiopia.

Methods: Semi-structured interviews were conducted with 24 patients, of whom 11 had been lost to follow-up and were non-persistent with ART. In addition, focus group discussions were performed with 15 ART nurses and 19 case managers. All interviews and focus groups were audio-recorded, transcribed, and coded for themes and patterns in Amharic using a grounded theory approach. The emergent concepts and categories were translated into English.

Results: Economic constraints, perceived stigma and discrimination, fasting, religious beliefs, medication side effects, and dissatisfaction with healthcare services were major reasons for patients being non-adherent and lost to follow-up. Disclosure of HIV status,

social support, use of reminder aids, responsibility for raising children, improved health on ART, and receiving education and counseling emerged as facilitators of adherence to ART.

Conclusions: Improving adherence and retention requires integration of enhanced treatment access with improved job and food security. Healthcare providers need to be supported to better equip patients to cope with the issues associated with ART. Development of social policies and cooperation between various agencies are required to facilitate optimal adherence to ART, patient retention, and improved patient outcomes.

6.2. Introduction

Antiretroviral therapy (ART) decreases progression to Acquired Immune Deficiency Syndrome (AIDS) and prolongs, and improves the quality of, life. Over 800,000 patients are living with Human Immunodeficiency Virus (HIV)/AIDS in Ethiopia and the prevalence of HIV/AIDS in the general population is estimated to be 1.5% [183]. In the past 8 years, decentralization and scale-up of the HIV care program have occurred and by the end of 2011, 249,174 adult patients (86% of eligible patients) had been prescribed ART.

Adherence to a medication regimen is defined by Cramer et al as "the act of conforming to the recommendations made by the provider with respect to timing, dosage, and frequency of medication taking" [88]. To optimize ART, at least 95% adherence is required in order to prevent the development of resistant viral strains, although regimens with boosted protease inhibitors (PIs) or non-nucleoside reverse transcriptase inhibitors (NNRTIs) can achieve good viral suppression even below this level of adherence [35]. Non-adherence to ART may result in regimen failure, immune

suppression, emergence of resistant viral strains, limited future treatment options, and higher treatment costs [89].

Adherence to a medication is a dynamic behaviour influenced by many factors. The findings of several studies conducted in resource-limited settings have shown that major facilitators of ART adherence encompass social support, positive treatment outcomes, and life-long projects [285-287]. Factors such as cost of medications, access to health facilities, transport costs, and fear of stigma and discrimination are recognized barriers to adherence with ART [225, 288, 289].

Achievement of optimal adherence and patient retention[290] are becoming the greatest challenges in the management of HIV/AIDS in Ethiopia. A five-year retrospective medical record review of 3012 adult patients who were enrolled in therapy at Gondar University Hospital ART clinic demonstrated that 31.4% had been lost to follow-up [189].

To our knowledge, only three qualitative studies have attempted to identify factors that influence adherence to ART in adult patients with HIV/AIDS in the Ethiopian setting. Financial constraints, distance to ART clinics, patient load, patients' beliefs, and alcohol and drug use were identified as barriers to retention in the Ethiopian healthcare setting [180, 181, 291]. Previous studies have mainly focused on exploring factors influencing patient retention at the healthcare level and were limited in their ability to identify barriers to, and facilitators of, medication adherence at the individual level. Moreover, none of these studies were performed in the Amhara region of Ethiopia, where 31.7% of the country's ART usage occurs [292]. The region is home to 20 million people, of whom more than 91% are Amhara and about 80% are Orthodox Christians [293]. This study

sought to examine the enablers and barriers to medication adherence to ART, including reasons for patients being lost to follow-up, in the Amhara region of Ethiopia.

6.3. Methods

6.3.1. Study Setting

This study was carried out at Felege-Hiwot Hospital and Gondar University Hospital, Northwest Ethiopia. Each hospital serves a catchment area of 5 million people. In 2005, when free ART was launched in the country, both hospitals began to offer ART. The numbers of patients receiving ART were 4,378 and 6,265, in Gondar University Hospital and Felege-Hiwot Hospital, respectively, at the time of data collection.

Adult patients with HIV-infection and CD4 count less than or equal to 350 cells/mm^3 regardless of the clinical symptoms, or with any symptoms indicating a WHO clinical stage of 3 or 4, irrespective of CD4 count, are eligible to start ART. At both hospitals, specific ART nurses provide counseling to patients diagnosed as HIV-positive before and after ART initiation, while the physicians working in the ART clinics initiate ART medication based on patients' clinical and laboratory findings. Nurses are also responsible for assessing patients' progress at regular appointments in ART clinics, every month for the initial six months and every three months thereafter. If patients have any complaints, such as opportunistic infections (OIs) and drug side effects, the nurses refer patients to the physician to receive treatment. Furthermore, the study clinics have a peer support program staffed with case managers who themselves take ART. ART nurses refer patients to case managers for adherence counseling and management of ART risk factors. Case managers are certified care providers responsible for managing ART risk factors and locating patients lost to follow-up. They carry out a

programmed outreach service to track patients who have been lost to follow-up and are not reachable by phone, and to provide onsite community support.

6.3.2. Inclusion/Exclusion criteria

Adult patients (≥18 years old) who had been receiving ART in the study clinics for at least a month and could provide informed consent in Amharic were eligible for the interviews. All ART nurses and case managers who had been working in the ART clinics for at least 6 months were invited to participate in the focus group discussions.

6.3.3. Recruitment and Sampling

ART nurses and case managers aware of patients' treatment histories, supplemented by checking of patients' medical records, helped to identify and recruit possible participants into the study. The recruitment of patients continued until information saturation was achieved. Research pharmacists working across the two sites invited all ART nurses and case managers to participate.

6.3.4. Ethics Statement

The Tasmanian Social Sciences Human Research Ethics Committee, University of Tasmania, Australia, and College of Medicine and Health Science Ethics committee, Bahir-Dar University, Ethiopia, approved this study. Patient interviews were conducted in private rooms where patients felt safe and stress-free. Focus group discussions were conducted in hospital auditoriums. Focus group participants were required to maintain the confidentiality of the identities of other participants and the content of the discussion. Participants were told either to remove themselves from the room or ask the interviewer to move the interview in another direction if they felt distress during the interview. The purpose of the study was explained to all participants using standard information statements, and written informed consent was obtained before

participation. At the end of the session, the participants received 150 birr (~ $ 7 USD) as compensation for their time and transportation costs. Patients who disclosed non-adherence during interview were referred to case managers in ART clinics for possible intervention. Personal or identifying information was not retained within the transcripts.

6.3.5. Data Collection

Data were collected from 22 February 2013 to 12 July 2013 using semi-structured interview and focus group discussion guides with patients and healthcare providers. The guides were designed to elicit information from the patients' and healthcare providers' points of view based on their experience with HIV medication, including factors that facilitate or constrain adherence to HIV medication and reasons for loss to follow-up. Consistent with an inductive approach, guides were updated continuously based on the results of the ongoing data analysis before the next interview or focus group discussion. A trained research pharmacist conducted the interviews and focus groups in the local language, Amharic. Comprehensive notes were taken throughout and after interviews and focus groups, and all sessions were audio-recorded. Participants decided on the times and the locations of the individual interviews. Data were stored in a locked cabinet in locked facilities in the College of Medicine and Health Sciences at the Bahir-Dar University. All electronic records were stored on a secure, password-protected, server at the University of Tasmania. Researchers were able access the data whenever required. Data will be destroyed 5 years following publication. Paper data will be securely shredded and electronic data will be erased at this time.

6.3.6. Data Preparation

Upon completion of each focus group and interview, the research pharmacist produced

a complete transcript in Amharic. The transcribed data were read and reviewed to ensure understanding and then compared with the original audio-records for accuracy. The study data were established from the transcripts.

6.4. Data Analysis

Analysis of data aimed to describe the barriers to, and facilitators of, adherence to ART including the possible reasons of patients for missing appointments and/or being lost to follow-up at ART clinics. A grounded theory approach was used for analysing the data [294]. The process of data analysis was as shown in **Figure 6**. The documents in Amharic were uploaded into NVivo (QSR, Cambridge, MA) and textual data were coded into themes inductively. Two coders (the research pharmacist and a general practitioner) performed the coding separately and differences were resolved with discussion. Focus groups and interviews were coded and analysed separately, and matched for common themes. The key findings were illustrated by selecting representative quotes.

Two bilingual translators translated emerging concepts and categories into English. The two translators discussed their differences and developed a single English version. A third person translated the final English version back into Amharic. A committee, consisting of an expert in English, a pharmacologist, an expert qualitative researcher and the research pharmacist, settled issues of conceptual equivalence and use of words between concepts and categories in Amharic and the final English version.

6.5. Results

6.5.1. Study Participants

Twenty-four patients, 15 nurses, and 19 case managers participated in this study. Forty-four face-to-face interviews and 6 focus group discussion sessions were conducted across the two sites.

Characteristics of Study Participants

Patients. The mean age of the patients was 36 years. Half of those who participated were women. Less than half (41%) were married or living with a partner, and 58% had primary school or no education. Approximately half (46%) had been lost to follow-up and returned to the ART clinics either through tracking or on their own. The remaining patients were on follow-up; of these, 69% never missed appointments and 31% missed appointments frequently.

Healthcare Providers. Approximately two-thirds (65%) of healthcare providers were women. The mean age of the healthcare providers was 32 years. Forty-four percent were nurses and the rest were case managers.

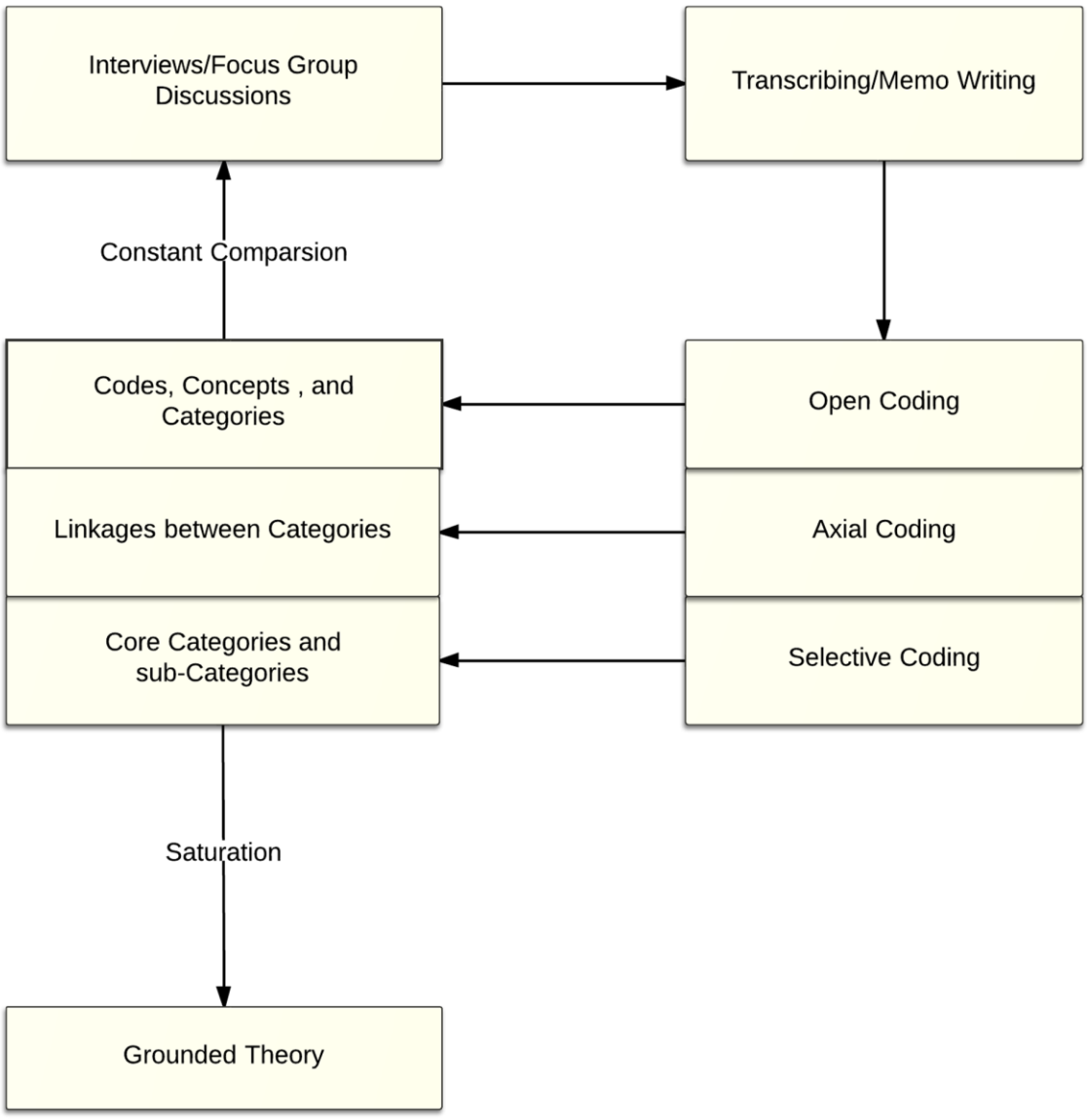


Figure 6. Data analysis in generating grounded theory.

Table 13. List of emergent themes that influence adherence to ART and retention in follow-up care.

Themes	Adherence facilitators	Adherence barriers	Factors influencing loss to follow-up
Theme I: Patient-Related			
• Economic constraints		✓	✓
• Disclosure and social support	✓		
• Reminders	✓		
• Stigma and discrimination		✓	✓
• Responsibility for raising children	✓		
• Religious rituals			
▪ Fasting		✓	
▪ Being baptized with holy water			✓
• Belief of being cured from HIV/AIDS			✓
Theme II: Healthcare Service-Related			
• Counselling and education	✓		
• Fatigue of healthcare providers		✓	
• Poor medical record handling		✓	
• Unavailability of office		✓	
• No service at weekends		✓	
Theme III: Medication-Related			
• Experiencing improved health on ART	✓		
• Adverse effects		✓	✓

6.5.2. Themes and Categories

The themes that emerged were classified as patient-related, healthcare service-related, and medication-related. Each theme was classified into categories as presented below and shown in Table 13.

6.5.2.1. Theme I: Patient-Related Factors

Patient-related factors such as economic constraints, disclosure of HIV status, social support, use of reminder tools, stigma and discrimination, responsibility to raise children, and religious rituals were the most significant determinants of adherence and loss to follow-up.

Category I: Economic Constraints

Individual interviews and focus groups indicated that movement for seeking employment and food insecurity impaired adherence to ART amongst patients with HIV/AIDS who had started ART. Almost all patients (11 of 12) who had been lost to follow-up were unemployed, daily laborers or waiters working at a low wage rate. They moved from one part of the country to another part of the country searching for a job. Lack of money for transport, unavailability of nearby ART clinic services, and language and communication barriers prevented such patients from remaining in care.

I went to Humera to find a job. I got one time a refill from Humera Hospital. After a while, I crossed the Sudan border with friends. I worked in the farm in a jungle for 2 months. I do not speak the Arabic language (so) I was not able to refill my medicine. On the way back to Ethiopia with friends, looters took all (my) money including (my) ART user identification card. Because of this, I missed my medication for about three months. (26 years, male, patient, casual worker, 008)

To get a job, patients usually move to remote areas where they cannot get access to ART. For instance, those who went to Sudan did not get the treatment there and were lost to follow-up for long period of time. (28 years, female, nurse, FG5)

Patients with HIV/AIDS reported reduced physical strength, especially in the initial phase of ART, and were only able to tolerate reduced work hours. Some patients generated a minimal monthly income not sufficient to cover the costs of their basic needs, including food. Thus, unavailability of food hindered patients from taking their HIV medications. Some of the patients, being dependent on the food supply from ART clinics, left their pill bottles with the nurses when they did not receive their food ration from the clinic. Some others patients believed that they had to consume costly food items to take their HIV medications.

Previously, I was getting (an) additional nutrition supply, plumpy nut, for free from the ART clinic. But the other day, the nurse told me that she would not give it to me anymore. When I heard this, I felt angry and left the medication bottle on the nurse's desk and went away from the clinic. Due to this I did not take pills for five days. (33 years, male, patient, jobless, 007)

When Non-Governmental Organizations (NGOs) stopped food donations, patients complain about continuing ART. Some of them are even lost to follow-up because of the unavailability of food. (32 years, female, case manager, FG3)

Most people do not have an idea that the medication can be taken eating any food available. They do not know that they can prepare the available food in the house with proper hygiene. They think the medicine will be harmful if they do not eat an expensive diet such as meat and eggs. (30 years, female, case manager, FG3)

Category II: Disclosure of HIV Status and Social Support

Both interview and focus group participants most frequently cited that disclosure of their HIV status to friends, family and neighbors was a facilitator of adherence. Patients who disclosed their HIV status to relatives and close friends did not fear stigma and discrimination to obtain and take drugs.

I have no problem of disclosing my (HIV) status to my family, friends, and others. When I usually introduce myself, I often tell them that I am living with HIV… this helped me to take the pills regularly, without any anxiety, and to recover from my illness as well. (35 years, female, patient, librarian, 015)

Many patients told me that disclosure of their status to neighbours and community helped them to take pills properly. (26 years, female, nurse, FG4)

Disclosing one's HIV status was found to be essential for receiving social support. Reminders to take pills, cover for transportation and food costs, and emotional backing were commonly reported. The most important way that patients received support was in reminders regarding the time they took pills. Patients received support usually from their partner, who himself/herself was also on ART, and/or children who were living with them. Experienced ART nurses and case managers noticed that transport and food support from NGOs had improved patients' attendance at ART clinics.

Sometimes when I feel fatigued, am busy with work or sleep at dose time my children remind me to take the pills. They bring me a glass of water and the medication bottle. (36 years, female, patient, casual worker, 004)

Aids from NGOs such as getting cooking oil, wheat, and soap until HIV patients recover

from their illness and support themselves is one facilitator for adherence to ART. (46 years, male, case manager, FG1)

Category III: Stigma and Discrimination

Patients and healthcare providers frequently mentioned that stigma and discrimination caused patients trouble in taking, obtaining, and keeping medications. Patients described how they would avoid taking pills in front of others, including family members who did not know their HIV status.

I used to miss pills many times… because people were with me. The guy with me did not know my HIV status. I worry what people think about me if they know about my status while I am taking pills in front of them. (25 years, female, patient, waitress, 020)

Only my mother knows about my HIV status… I fear stigma and discrimination if other family members noticed me taking the pills. (20 years, female, patient, waitress, 006)

Patients also preferred to attend treatment in clinics far away from home to avoid disclosure of their HIV status to their community members.

Fearing disclosure in their residential area…. patients attend ART from Gondar when they have access to it in Bahir-Dar and vice versa. That creates a challenge for patients in picking up their medicine later. (23 years, male, nurse, FG1)

Lack of privacy was a particular challenge for patients working in a private home or organization. Half of the patients were part-time workers, daily labourers or waiters. These patients were forced to work at a low wage rate for long hours to cover their living costs in places where their privacy could not be maintained. They had problems with finding a place to keep and take their medications; they thought that they had to

hide their pills from employers and colleagues. Patients felt that they might be dismissed from their job if employers learned of their status.

If the employer learns that I am living with HIV… I fear to be sacked from my job. (26 years, female, patient, casual worker, 019)

When I asked my patient, how she was taking her pills? Whether she kept her time or not… she told me that she is a daily laborer baking injera and abshilo in other people's houses. If employers learn that she is living with HIV and taking the pills they would stop her working with them. She used to take pills only when they went away from her and she was alone. As the result she does not take her pills on time. (45 years, female, nurse, FG5)

I was working as a cooker in a cement factory compound for Indian employees. For some time, I was taking the pills hiding myself (so as) not to be noticed by anyone. But, later, I became worried thinking that if they knew my status, they might dismiss me from my job. Then I stopped taking the pills. (27 years, female, patient, cohabiting, 018)

Category IV: Responsibility for Raising Children

Patients' commitment to raise and educate their children facilitated medication taking. Patients with HIV were at the peak of their reproductive lives; 14 out of 24 (mean age 36) had dependent children. They fear passing away with AIDS, leaving their children as orphans. Of 14 patients who were living with their children, 9 were found to be adherent by their ART nurses.

… I have a boy born free of the virus. As long as I am alive, I wish to see him achieving better opportunities. If I am not taking the medication properly or abandoned it altogether, I am ruining his chance. (35 years, male, patient, self-employed, 002)

Patients usually say that if they are not alive, it is difficult to imagine the survival of their children. They told me that the medicine kept them healthy to work and help their children to achieve a better future. (35 years, male, nurse, FG5)

Category V: Reminders

Patients frequently mentioned that setting alarms on watches or mobile phones helped them to remember to take their pills. Seven respondents said they set alarms on their mobile phones or watches. Providers also stressed the benefit of reminders in avoiding pill missing due to hectic daily activity.

To take my pills on time, I set a reminder on my mobile phone…it reminds me of the time of my medication even when I forget it. (41 years, male, patient, casual worker, 016)

Especially use of mobile phones or watch alarm tones is more sustainable for not forgetting taking pills. (27 years, female, case manager, FG6)

Although electronic reminder tools have the aforementioned advantages, some patients did not have their own mobile phone or watch, and some others were too illiterate to use these reminder tools. Eight respondents had no formal education and were not able to write and read. These patients used other alternative reminders such as the position of the sun, length of shadows, entrance and exit time of domestic animals and students, and bells from a church or mosque or factories to take their pills on time. Although such kinds of devices were helpful as pill reminders, they were limited in their ability to indicate the exact time.

I take pills whenever I hear Allah Akbar. (26 years, male, patient, casual worker, 008)

I have an old lady customer who is too illiterate to read a watch and who has no family or

relatives living with her…she usually takes her pills looking at students going to school in the morning. (33 years, male, nurse, FG5)

Category VI: Religious Rituals

Religious rituals like fasting and holy water were found to influence medication taking. Both Ethiopian Orthodox Christian followers and Muslims have several fasting days and seasons within a year.

Sub-category I: Fasting

During fasting seasons, some patients did not take their medications properly.

I take the morning dose at midday during fasting since I have to wait without any meal until midday. (38 years, female, patient, secretary, 023)

(Orthodox Christian) patients have a strong attitude towards fasting and become late in taking pills on Friday and Wednesday or in any fasting season. Patients take the morning dose at 12 am. (52 years, male, case manager, FG3)

During Ramadan, I only take the evening dose. It is impossible to take the morning dose as we eat during the night-time. (38 years, male, patient, driver, 024)

During Ramadan some Muslims do not take the daytime dose. They only take the evening dose while taking their food. They usually come and consult us on what to do. (40 years, female, nurse, FG2)

Sub-category II: Being Baptized with Holy Water

Going to monasteries to be baptized with holy water was the most frequently mentioned reason for patients being lost to follow-up. This was reported by five of the

11 patients lost to follow-up; all of them were females. Some Orthodox priests preached that patients should take holy water, pray to God, and stop taking their pills to be cured of their 'curse'.

I stopped taking my medication while I started being baptized with holy water (in a monastery). Priests there told us only to be baptized by the holy water and stop taking antiretroviral pills; I believed in Jesus and took only the holy water to be cured. (20 years, female, patient, waitress, 006)

Patients preferred complete cure from HIV/AIDS with the holy water treatment rather than taking pills throughout their life. Interviewees and focus group members reported discontinuation of ART treatment in those being baptized with holy water.

I have friends who were living with HIV; they told me that they get cured after attending holy water treatment for three months in a monastery. They told me to go and get the treatment; in addition I have been informed to stop the pills citing that I do not have to believe in the two things simultaneously to be cured. I left my pills at home and went there for two months. (24 years, female, patient, waitress, 022)

During the time when I was tracking lost patients, members of a lost patient's family told me that she is cured from her disease after she had been baptized from a monastery holy water. They tried to convince me to go and check her health status. Still now she has not come back to the clinic. (31 years, female, case manager, FG2)

Some of the patients were lost to follow-up after they were baptized by the holy water; they told us that they are cured from HIV/AIDS because of the holy water. (36 years, male, nurse, FG5)

6.5.2.2. Theme II: Healthcare-Related Factors

Healthcare-related factors, such as patient education and counselling facilitated medication adherence, while busyness of healthcare providers, poor laboratory service, and poor medical record handling impaired adherence and retention.

Category I: Counselling and Education

Education and counselling of patients in the ART clinics motivated them to take their pills. Case managers and ART nurses provided education, which focused on the importance of perfect adherence, strategies to improve adherence, consequences of non-adherence, possible side effects of the medications, and the duration of treatment required.

Every morning in the waiting room nurses and case managers teach us the consequences of not taking pills properly and the benefits of disclosure to family and the community. That helps me a lot to adhere to the treatment and improves my health condition. (36 years, female, patient, self-employed, 014)

If the healthcare provider who initiated ART gives comprehensive education, including how long the medications will be taken, the possible side effects of the medications, the importance of the treatment, whether it cures or not, and checks patients' understanding at the end, it will help patients to continue their treatment without interruption. (28 years, female, nurse, FG5)

Category II: Fatigue of Healthcare Providers

In contrast, healthcare providers were fatigued with a high load of patients; this impaired the quality of the service delivered. Sometimes, it was felt that ART nurses did

not have empathy and rushed when writing prescriptions, without addressing patients' concerns about their treatment. This impaired the ART nurse-patient relationship and patients did not enjoy coming to the clinics.

They abuse you, they do not accept you in good terms, and I feel bad about these (things). Even, I feel my illness more when I come to the clinic and see their faces. I feel as if I went to a police station and was interrogated as a criminal. (38 years, female, patient, secretary, 023)

…The hospital is crowded … it has many patients… professionals are fatigued with it. (52 years, male, case manager, FG3)

Category III: Poor Laboratory Service

The ART clinics have large numbers of patients; there are queues to receive services. Patients were instructed to come to ART clinics early in the morning and line up to have their CD4 counts checked. Some of them were too busy to do so and unable to attend to their treatment properly.

I came (to the ART clinic) early in the morning at 5 am to get a CD4 test. We were forced to struggle with the coldness and thieves at this time. This is the reason why I did not check my CD4 count regularly and attend my treatment properly. (38 years, female, patient, secretary, 023)

The result of CD4 count tests are delayed up to one day after the test; this needs to be corrected. (28 years, female, case manager, FG6)

Category IV: Poor Medical Record Handling

Several patients and healthcare providers mentioned that there have been serious problems in handling of patients' medical records in the hospitals. Many patients experienced loss of their medical record and were forced to start a new medical record, losing all their previous data. Sometimes patients were forced to repeat CD4 count measures when the laboratory report was lost from the medical record and was therefore unavailable to inform medical decisions.

My chart was lost from the chart room…the nurse told me to I needed a new chart but I was not voluntary to have a new one…I left the clinic citing the need for my previous documents for prescribing of my medications. (35 years, male, patient, self-employed, 002)

There is problem of chart loss. Sometimes you find the empty cover of the chart while all the documents are lost. Patients were forced to repeat CD4 tests as a result. (36 years, female, case manager, FG2)

6.5.2.3. Theme III: Medication-Related Factors

Improvements of health on ART and medication side effects were the two consistent and contrasting themes related to medication. Improvement of health on ART facilitated adherence to HIV medication, while medication side effects was among the reasons for patients to be non-adherent or lost to follow-up.

Category I: Improved Health on ART

Most patients had been confirmed as HIV-positive after suffering a long-term sickness. They had seen the devastating effect of HIV on their bodies and had vivid illnesses and stories. A significant improvement of health witnessed soon after initiating ART heightened trust in the medications.

Both patients and providers highlighted being healthy, improved appetite, increased weight and CD4 count, and prolonged lives as positive treatment outcomes. Patients were no longer bedridden, had strength, resumed work, and increased their incomes. These improvements inspired them to continue taking their medicines.

I have decided to be more committed towards the treatment because I have seen the benefits of antiretrovirals. My appetite has improved, I was bedridden, but now I am healthy and I usually find myself at the field for work…. I achieved all this because of the pills. Hence, I should not stop taking the pills. (35 years, male, patient, farmer, 016)

… Improvement of health after treatment of OIs, being able to live longer and progressive increments of CD4 counts were the major factors strengthening medication taking. (24 years, male, nurse, FG5)

Category II: Adverse Effects

Patients who experienced unanticipated and/or intolerable side effects, like nightmares and psychosis, missed doses or discontinued therapy altogether. This was particularly likely among patients who had started ART when asymptomatic as they considered the medications had worsened their health.

I was not conscious (after taking the medications), I was mad, as neighbours told me. I went to a neighbour's house and shouted, calling on a certain woman, blaming her for being evil eye and making me sick. After that I stopped taking the pills. (26 years, female, patient, casual worker, 019)

When I phoned a lost patient who was on TDF/3TC/EFV, for tracking, he told me that he could not come back unless the regimen changed. That was because he had developed

nightmares due to the efavirenz. (33 years, male, case manager, FG2)

At the beginning of my treatment, I experienced vomiting. As the result, I missed some doses, until I adapted to the medication. (30 years, female, patient, waitress, 009)

6.6. Discussion

We sought to understand the barriers and facilitators that influence adherence in patients taking ART in the Amhara region of Ethiopia. We identified economic constraints as the greatest barrier, with fear of stigma and discrimination, fasting and holy water, poor healthcare services, and medication side effects also interfering. Meanwhile, disclosure of HIV status, social support, use of reminders, life-long projects, counselling and education, and improved health on ART facilitated medication adherence and retention in HIV care. Most of these factors were consistent with the findings reported in other regions of Ethiopia [180, 181, 291] and elsewhere in resource-limited settings [192, 193, 295]. However, some of the findings such as migration [296-300], holy water, fasting [295], and traditional time reminders have been rarely reported or not reported at all in other settings. These differences may be attributed to the socio-economic and socio-cultural differences of our study sample. The major findings that had significant impact on adherence including economic constraints, stigma and discrimination, and disclosure of HIV status and the new or the rarely reported findings highlighted above are discussed below.

The two major socio-economic constraints that negatively affected adherence and retention in HIV care in our study were a lack of work, resulting in the need for migration to find a job, and food insecurity. These factors have also been documented in other studies [288, 295-297, 299-302]. Patients were lost to follow-up when they

migrated to other places either inside or outside Ethiopia to find a job. Migration of Ethiopian youths in large numbers from rural to urban areas of the country to find work, as well as out of the country to the Middle East and sub-Saharan African countries, has been reported by other authors [303, 304]. Patients also missed pills and stopped collecting repeat prescriptions from clinics when they could not afford to buy food, or when NGOs stopped supplying food rations. The negative impact of food insecurity on adherence has also been recognized in other studies conducted in sub-Saharan Africa [288, 301, 302]. Lack of job opportunities and food insecurity, while not exceptional to patients with HIV/AIDS, were exacerbated by the co-existence of other HIV-associated challenges such as stigma and discrimination, reduced physical activity, medication schedules, and indirect treatment costs. Proactive strategies to improve access to jobs and food security for patients taking ART are required in Ethiopia. Both governmental and non-governmental organizations need to work in coordination to address the multilayered disadvantages in patients receiving ART.

Socio-cultural factors, such as stigma and discrimination and religious rituals, also had undesirable effects on medication adherence and remaining in care in this sample. Stigmatization and discrimination are complex socio-cultural phenomena that arise from the perception that a person with HIV/AIDS has unwanted qualities, thus reducing him/her in the eye of society [305]. Perceived stigma (felt stigma) and discrimination and lack of privacy to take and collect medication hindered adherence to ART in this study; these factors were also identified in other sub-Saharan and Far-East Asian studies [147, 170, 295, 306-308]. As reported by other authors [300], patients in this study had concerns about being stigmatized and losing their jobs if their HIV status was discovered when they took pills in front of work colleagues or asked permission from

their employers to collect medications at appointment dates. Seeking treatment at health facilities far away from home to hide their HIV status from family and colleagues is consistent with findings of other qualitative studies [295, 309].

A multi-faceted intervention, including information provision, skill building, counselling and facilitating interaction between people with HIV/AIDS and the community, has the potential to reduce stigma and improve ART adherence and retention in care [310-312]. A systematic review by Stangl et al. [310] reported that there was a lack of effective stigma reduction strategies that could be implemented on a large scale. Tackling stigma and discrimination at multiple levels might also improve patients' abilities to adhere to ART treatment and continue presenting for medical care in Ethiopia.

Religious beliefs are complex cultural concepts and influenced patients' treatment with antiretrovirals in our sample of study; this has been reported elsewhere [295, 313, 314]. The Ethiopian Orthodox Church does not allow eating until midday every Wednesday and Friday, as well as in fasting seasons such as Flseta and Worha-Tsom. Similarly, Muslims do not eat during the daytime in Ramadan. Patients miss or delay medications to fulfill these religious obligations. Going to monasteries to be baptized with holy water was found to be the most important reason for patients being lost to follow-up in this study. Another study in Ethiopia has also found seeking traditional treatment and/or holy water treatment to be the most important reason for patients being lost to follow-up care [315]. Stakeholders, governmental and non-governmental, should work with religious authorities to reduce the negative impact of fasting and holy water on medication-taking.

Disclosure of HIV status, social support, and use of reminders were identified as important facilitators of adherence in this study; other studies have reported similar

findings [119, 155, 156, 295, 316-319]. Case managers and ART nurses encouraged patients to disclose their HIV status to family members or close friends who can provide them social support, reminders about pills, financial assistance, and emotional backing to facilitate medication taking in our study and elsewhere [179, 192, 287, 320]. Case managers at the clinics are also working to deliver emotional support and resolve patients' problems based on their experiences living with HIV. Intervention studies reported that integration of dialogue and thinking about what needs to be done prior to disclosure, role-playing, and behavioural exercise were more effective than separate interventions in promoting disclosure [321, 322]. There appears to be a role for these types of interventions to enhance disclosure of HIV status and therefore aid in the achievement of optimal adherence and retention in care in Ethiopian patients taking ART as well.

One facilitator of medication adherence was the use of electronic devices, such as mobile phones and alarms. These have the advantage of reminding patients of their medication times without the need for disclosure of their HIV status to others. Access to mobile phones is increasing in Ethiopia [323] and setting alarm tones on mobile phones helped patients to remember to take pills. Randomized controlled trials in Kenya reported a mobile phone short message service improved adherence to ART treatment and retention in medical care [155, 156]. Healthcare providers need to use the opportunity of increasing access to mobile phones in the local area [323] for improving patients' adherence to HIV medication. Illiterate patients used the position of the sun, entrance and exit time of students, and the bell or sound of prayer time as their reminder to take pills. This finding is unique; no other studies have reported the use of the aforementioned traditional ways of time measuring for taking pills. Given many

Ethiopian HIV-positive patients are illiterate [324] and depend on traditional ways of time counting, which do not measure point to point medication time and influenced by many factors, the healthcare providers need to train patients how to use the simple electronic reminder devices to improve adherence.

6.7. Strengths and Limitations

One of the primary strengths of this study was the use of multiple data sources including focus group discussions and semi-structured interviews, involving patients on ART, ART nurses, and case managers across two sites. Almost all participants accepted our offer and were involved in the study; the non-response rate was very low. This may have been due to scarcity of this kind of research in our region of Ethiopia, and thus this research gave an opportunity for participants to share their experiences of ART. Both patients, who were adherent and non-adherent, including those who had been lost to follow-up from ART clinics, were included in this study.

The study has some limitations. People who were picking up medications for someone else were not included in this study. Moreover, patients who were bedridden or with psychiatric or other problems who were not able to attend ART clinics at the times of data collection were not interviewed.

6.8. Conclusion

Scale-up of treatment and care for patients with HIV/AIDS in sub-Saharan Africa has been a decisive clinical achievement. The full benefit of the scale-up cannot be realized without achieving long-term optimal adherence and retention in care. In this study we found that economic constraints, perceived stigma and discrimination, fasting, holy water, and poor healthcare services hamper adherence to ART and retention in care.

Conversely, disclosure of HIV status, social support, use of reminder aids, having life-long projects, and patient education and counselling facilitated adherence and retention in care. International studies have demonstrated that interventions directed at many of these factors have encouraged patients to achieve optimal adherence and remain in care. Interventions integrating enhanced treatment access with improved job and food security, supporting healthcare providers, development of social policies, and cooperation between various agencies are required to facilitate optimal adherence to ART, retention in care, and improved patient outcomes.

CHAPTER SEVEN

7. ADHERENCE TO ANTIRETROVIRAL THERAPY AND VIROLOGIC FAILURE: A META-ANALYSIS

7.1. Abstract

The often cited need to achieve ≥95% (nearly perfect) adherence to antiretroviral therapy (ART) for successful virologic outcomes in HIV may present a barrier to initiation of therapy in the early stages of HIV. This meta-analysis synthesised 43 studies (27,905 participants) performed across more than 26 countries, to determine the relationship between cut-off point for optimal adherence to ART and virologic outcomes. Meta-analysis was performed using a random-effect model to calculate pooled odds ratios with corresponding 95% confidence intervals. The mean rate of patients reporting optimal adherence was 63.4%. Compared with suboptimal adherence, optimal adherence was associated with a lower risk of virologic failure (0.34; 95% CI: 0.26-0.44). There were no significant differences in the pooled odds ratios among different optimal adherence thresholds (≥98-100%, ≥95%, ≥80-90%). Study design (randomised controlled trial versus observational study) (regression coefficient 0.74, 95% CI: 0.04 - 1.43, p< 0.05) and study region (developing versus developed countries; regression coefficient 0.56, 95% CI: 0.01-1.12, p<0.05) remained as independent predictors of between-study heterogeneity, with more patients with optimal adherence from developing countries or randomised controlled trials experiencing virologic failure. The threshold for optimal adherence to achieve better virologic outcomes appears to be wider than the commonly used cut-off point (≥95%

adherence). The cut-off point for optimal adherence could be redefined to a slightly lower level to encourage the prescribing of ART at an early stage of HIV infection.

7.2. Introduction

HIV/AIDS has been transformed into a manageable chronic disease with the advent of combination antiretroviral therapy (ART) initiated as the standard of care [325]. Three classes of HIV medications have been widely used in combination - nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) [325]. Despite the availability of effective treatment options, suboptimal adherence to treatment can result in insufficient viral suppression and promote the emergence of drug-resistant viral strains, resulting in regimen failure, progression to AIDS, and death [220, 221, 326]. Paterson et al. [89] suggested that at least 95% adherence to unboosted PIs was required for virologic suppression. This 95% adherence cut-off point, based on what is now obsolete therapy, has been widely used as the level of optimal adherence needed to be met by patients taking newer agents and their combinations. The concern that patients may not achieve a near perfect adherence presents a barrier for initiation of therapy in the early stages of HIV [327].

This meta-analysis integrated finding from observational studies on ART adherence with two objectives: (a) to critically evaluate the association between optimal adherence to ART and virologic outcomes, and (b) to use meta-regression to determine methodological, regimen, and population factors that could moderate the relationship between adherence and virologic outcomes.

7.3. Methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement in conducting this meta-analysis [328]. Studies eligible for inclusion were randomised controlled trials, retrospective analyses of data from trials, and cohort studies measuring the relationship between medication adherence to ART and virologic failure.

7.3.1. Search Strategy

WB carried out systematic literature searches of the electronic databases MEDLINE via PubMed, Cochrane Clinical Trials, and EMBASE from their inception date to 17 April 2015. This search used combinations of the following key words: medication adherence, patient compliance, antiretroviral therapy, antiretroviral agent, antiretroviral treatment, protease inhibitors, non-nucleoside reverse transcriptase inhibitors, virologic failure, and viral load. The reference lists of all articles included in this meta-analysis were also searched. Review articles, editorials, commentaries, government reports, and guidelines were excluded from this review. Titles and abstracts of potentially relevant articles were screened independently by WB and YM. Full articles of potentially appropriate citations were screened for inclusion in this review if they fulfilled the following criteria: original research, participants aged 16 years or older, having a clear definition of medication adherence measurement and clear cut-off points for optimal and suboptimal adherence, and virologic failure stratified by optimal and suboptimal medication adherence groups. Ethical approval was not required as this study was based on published data and had no direct access to patient information.

7.3.2. Data collection and outcome measures

WB extracted data using standardised forms, with recording of authors, year of publication, country of study, study type, regimen, method of adherence measurement, cut-off points for good adherence and virologic failure. The data were verified by a second reviewer (YM). Disagreements between reviewers were resolved through discussion until a consensus was reached. Study authors' grouping of patients into optimal and suboptimal adherence using the most objective measure was used. When a study reported more than one adherence measurement, the most reliable adherence measurement data was used, with reliability defined in following order: Medication event monitoring system (MEMS) > pill count > pharmacy refill > self-reported adherence in the past week > self-reported adherence in the past month. When the number of virologic failures within each adherence group was not reported, we calculated virologic failure from the information provided in the paper or contacted the corresponding author. Studies were excluded when it was not possible to obtain virologic failure data in each adherence group. The United Nations Human Development Index (HDI) ranking was used to categorise studies into low and high human development groups [329].

7.4. Statistical analysis

The data were analysed using Review Manager (RevMan) version 5.3 (Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, 2014) and Comprehensive Meta-Analysis (CMA) version 3.3.070 (Biostat, Englewood, NJ, USA, 2014). Each class of antiretroviral was considered in a separate analysis of the association between adherence and virologic failure in randomised clinical trials. Results are presented based on nine categories, including study region, antiretroviral regimen, treatment

experience, virologic failure cut-off points, adherence cut-off points, adherence measurement, study design, observation period, and year of publication. Adherence pooled odds ratios and 95% confidence intervals were calculated using a random effect model (DerSimonian and Lard) [330] that accommodated the random variation within studies and between-studies [331].

Heterogeneity between-studies were examined using the Q and I^2 statistics [330, 332]. The odds ratio was plotted against the inverse of standard error to identify the risk of publication bias by visually assessing the symmetry of funnel plots. Statistical significance was confirmed using Egger's test [333], with a p value less than 0.05 considered suggestive of publication bias. A meta-regression was performed to examine major moderators of the between-studies heterogeneity. Results with p-values less than 0.1 from univariate analyses were included in the multivariate meta-regression model.

7.5. Results

Overall, 1,796 studies were identified, of which 1,449 were excluded after review of the title and abstract Figure 7. The full text of the remaining 347 citations was screened, and 43 studies with 27,905 participants met the inclusion criteria. The included studies had wide a variation in sample sizes (range=34-3,607, mean=649, SD=805) and a slight majority of participants were male (57%). Twenty-five studies were prospective studies [89, 157, 218, 235, 244, 334-354] that reported virologic failure according to adherence group. The remaining studies were randomised controlled trials (11) [187, 355-364] and retrospective studies (7) [234, 365-370]. Characteristics of the included studies are shown in Table 14.

With respect to location, 14 studies were conducted in sub-Saharan Africa; 9 in the US; 6 in Canada; 5 in Europe; 5 in Asia; 1 in Australia; and 3 studies in multiple countries.

Twenty-two (49%) studies included only treatment-naïve patients and the remaining 21 studies included both treatment-naïve and/or treatment-experienced patients. All studies reported cut-off points for optimal adherence and virologic failure. Thirty studies (70%) defined optimal adherence as ≥95%, with the remainder using 100%, 98%, 90%, 85% and 80% as the cut-off points. Optimal adherence rates varied greatly across studies, partially due to the use of these different cut-off points and also different methods of measurement to assess adherence. The mean rate of achieving optimal adherence in adults was 63.4% (standard deviation (SD)=23.7, range 5% to 97%, n=43).

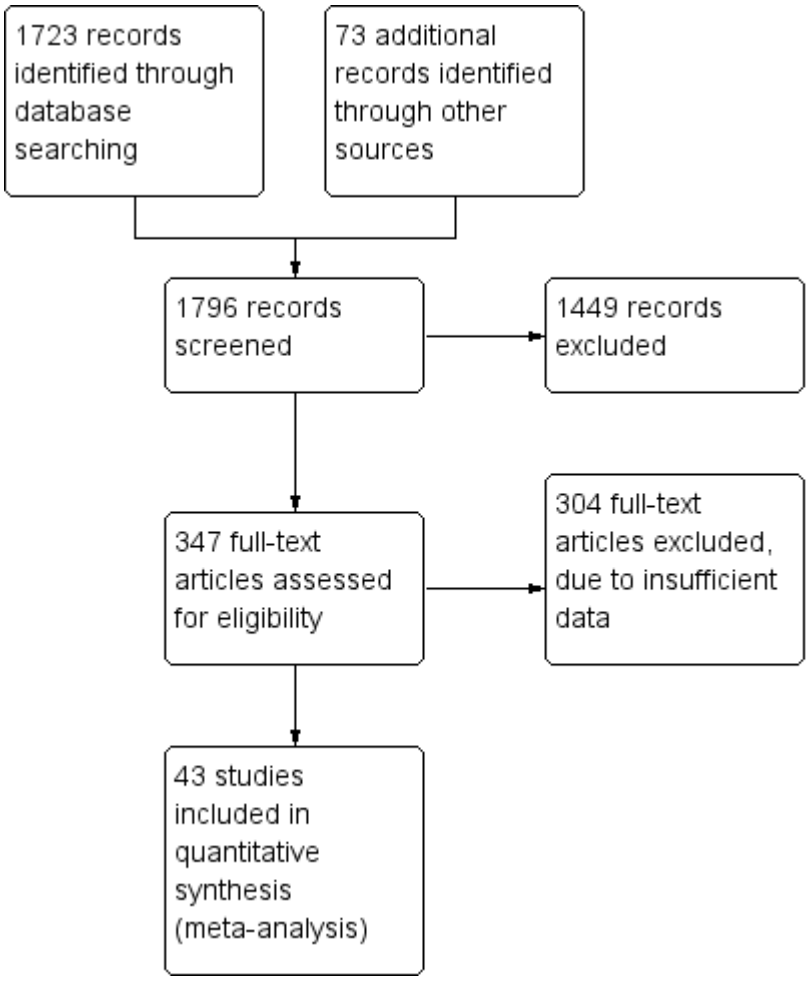


Figure 7. Study selection used in the meta-analysis

Table 14. Characteristics of included studies in meta-analysis of adherence to antiretroviral therapy and virologic failure.

Study	Country	Study type	Definition of virologic failure (copies/mL)	Adherence measures	Cut-off point for good adherence %	Observation period
Pasternak et al. 2012 [355]	Netherlands	Randomised controlled trial	≥50	MEMS*	100	9 months
Okonjio et al. 2012 [356]	Kenya	Randomised controlled trial	≥400	Pill count	≥95	24 weeks
Murphy et al. 2012 [365]	South Africa	Retrospective study	≥50	Pharmacy refill	>90	24 months
Nolan et al. 2011 [366]	Canada	Retrospective study	≥500	Pharmacy refill	≥95	median 51 months
El-Khatib et al. 2011b [367]	South Africa	Retrospective study	>50	Pharmacy refill	≥95	median 44 months
Messou et al. 2011 [334]	Côte d'Ivoire	Prospective study	≥300	Pharmacy refill	≥95	12 months
Lima et al. 2010 [368]	Canada	Retrospective study	>400	Pharmacy refill	≥95	median 2 years
Ford et al. 2010 [157]	South Africa	Prospective study	>5000	Self-report	≥95	5 years
Nellen et al. 2009 [335]	Netherlands	Prospective study	>400	Pharmacy refill	≥85	2 years
San et al. 2008 [336]	Mozambique	Prospective study	≥1000	Pill count	>95	1 year

Study	Country	Study type	Definition of virologic failure (copies/mL)	Adherence measures	Cut-off point for good adherence %	Observation period
Nachega et al. 2007 [218]	South Africa	Prospective study	>400	Pharmacy refill	100	median 2.2 years
Gross et al. 2006 [338]	Canada	Prospective study	>1000	Pharmacy refill	>95	median 29 months
Moore et al. 2005 [337]	Canada	Prospective study	≥500	Pharmacy refill	>95	median 44.7 months
Kitahata et al. 2004 [369]	USA	Retrospective study	>500	Pharmacy refill	>90	median 89 weeks
Cahn et al. 2004 [357]	Argentina, Brazil, Mexico, Italy, Thailand, Canada	Randomised controlled trial	≥400	Self-report	≥95	48 weeks
Arnsten et al. 2001 [244]	USA	Prospective study	>500	MEMS	≥90	5.1 months
McNabb et al. 2001[339]	USA	Prospective study	≥400	MEMS	>95	3 months
Parienti et al. 2010 [340]	USA	Prospective study	≥50 (400)	MEMS	>95	2 years
Bangsberg et al. 2000 [341]	USA	Prospective study	≥400	MEMS	≥98	median 9.4 weeks
Paterson et al. 2000 [89]	USA	Prospective study	≥400	MEMS	≥95	median 6 months
Tuldra et al. 2000	Spain	Randomised	>400	Self-report	≥95	48 weeks

Study	Country	Study type	Definition of virologic failure (copies/mL)	Adherence measures	Cut-off point for good adherence %	Observation period
[364]		controlled trial				
Meresse et al. 2013 [358]	Cameroon	Randomised controlled trial	≥40	Self-report	≥80	24 months
Abah et al. 2014 [370]	Nigeria	Retrospective study	>1000	Pharmacy refill	≥95	median 12 months
Neogi et al. 2013 [342]	India	Prospective study	>400	Self-report	100	2 years
Li et al 2012. [343]	USA	Prospective study	≥200	Self-report and Pill count	≥95	32 months
McMahon et al. 2013 [234]	India	Retrospective study	≥200	Pharmacy refill	>95	12 months
Ekstrand et al. 2011 [344]	India	Prospective study	>1000	Self-report	≥95	2 years
Lower-Beer et al. 2000 [345]	Canada	Prospective study	>500	Pharmacy refill	≥95	median 19 months
Carr et al. 2000 [187]	Australia	Randomised controlled trial	≥50	Self-report	100	52 months
Cohen et al. 2013 [359]	21 countries	Randomised controlled trial	≥50	Self-report	>95	96 weeks
Haubrich et al. 1999 [360]	USA	Randomised controlled trial	<500	Self-report	≥95	6 months
Muyingo et al. 2008	Uganda and	Randomised	>50 (400)	Pharmacy refill	100	48 weeks

Study	Country	Study type	Definition of virologic failure (copies/mL)	Adherence measures	Cut-off point for good adherence %	Observation period
[361]	Zimbabwe	controlled trial				
Anude et al. 2013 [346]	Nigeria	Prospective study	≥400	Pharmacy refill	≥95	12 months
Nelson et al. 2010 [362]	26 countries	Randomised controlled trial	≥50	Self-report	>95	96 weeks
Biswas et al. 2014 [347]	USA	Prospective study	≥40	Self-report	>95	3 years
Ti et al. 2014 [349]	Canada	Prospective study	≥500	Pharmacy refill	≥95	median 32 months
El-Khatib et al. 2011b [348]	South Africa	Prospective study	≥400	Pill count	≥95	24 weeks
Glass et al. 2006 [350]	Switzerland	Prospective study	≥50 (400)	Self-report	≥95	12 months
Jordan et al. 2009 [351]	Vietnam	Prospective study	≥1000	Self-report	≥95	16.65 months
Goldman et al. 2008 [352]	Zambia	Prospective study	≥400	Pharmacy refill	≥95	744 days
Court et al. 2014 [353]	South Africa	Prospective study	>1000 copies/mL	Pharmacy refill	≥90%	27 months
Shet et al. 2014 [363]	India	Randomised controlled trial	>400 copies/mL	Pill count	≥95%	96 weeks
Carrieri et al. 2003 [354]	France	Prospective study	200, 400, 500 copies/mL	Self-report	100%	36 months

7.5.1. Meta-analysis and Meta-regression

Of a total 27,905 participants, 22,740 participants had a viral load and adherence measurement; 7,056 (31%) had virologic failure. Overall, 3,464 of 15,067 participants with optimal adherence to ART (23%), and 3,592 of 7,673 participants with suboptimal adherence (47%) had virologic failure (Figure 8). The pooled odds ratio for virologic failure for optimal adherence compared to suboptimal adherence was 0.34 (95% CI: 0.26-0.44). A high degree of heterogeneity was found: Q statistic P<0.001 and I^2 =90%. The funnel plot did not show asymmetry (Figure 9), and the result of Egger's test was not statistically significant (p=0.68). We conducted subgroup analyses to recalculate the pooled odds ratio according to study design, HDI rank, regimen, treatment experience, viral load cut-off points, adherence measurement, and adherence cut-off points (Table 15).

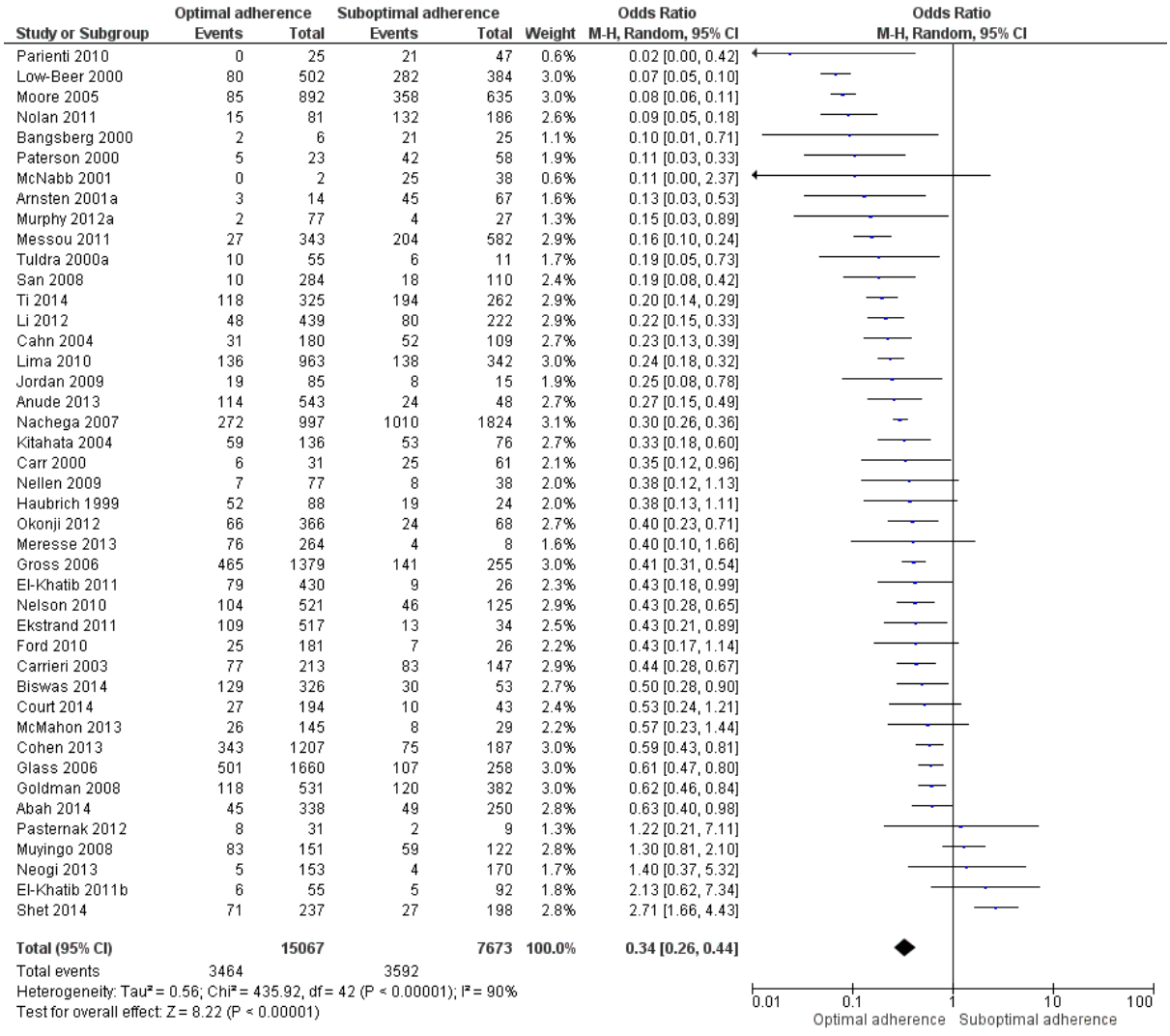


Figure 10. Association between adherence to antiretroviral therapy and virologic failure.

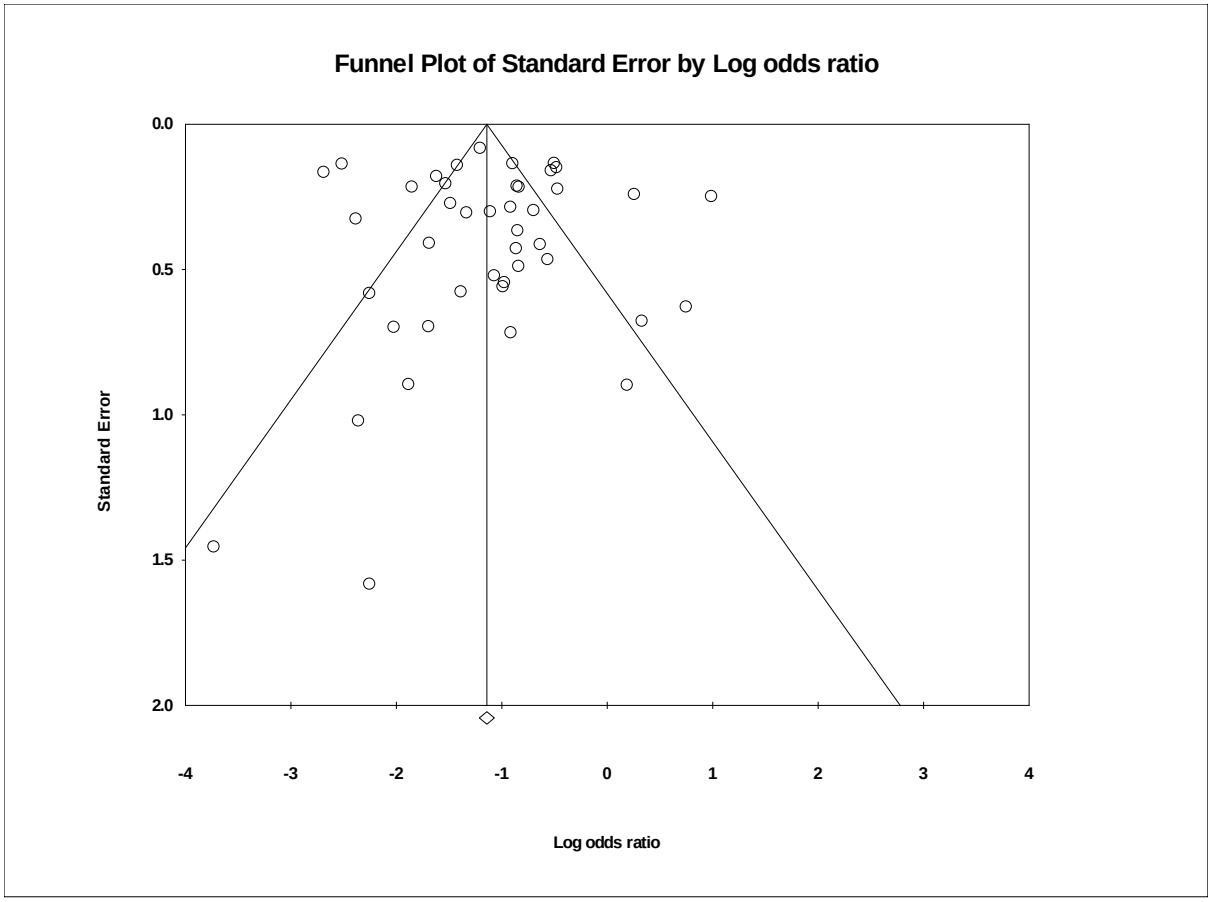


Figure 11. Funnel plot for the association between adherence to antiretroviral therapy and virologic failure (p=0.68 at Egger's test).

The results of univariate meta-regression analyses for different moderators are shown in Table 16. Based on virologic failure cut-off points, studies were classified into three sets including: ≤100 copies/mL, 11 studies (N=5,646); between 100 copies/mL and 400 copies/mL, 17 studies (N=9,351); and between 500 copies/mL and 1000 copies/mL, 14 studies (N=7,383). The pooled odds ratio for virologic failure for optimal adherence compared to suboptimal adherence for the studies with the lowest virologic failure cut-off was higher (0.55; 95% CI: 0.41-0.74, I^2=56%) than for the studies with an intermediate virologic failure cut-off (0.37; 95% CI: 0.26-0.54, I^2=88%). The group using a virologic failure cut-off greater than 500 copies/mL had the lowest pooled odds ratio for virologic failure (0.25; 95% CI: 0.16-0.41, I^2=92%). Studies with the lowest virologic

failure cut-off reported a significantly different pooled odds ratio compared with studies with a virologic failure cut-off greater than 500 copies/mL (regression coefficient -0.75; 95% CI: -1.39 - -0.12, p=0.02).

According to participants' treatment experience, studies were grouped into three sets: treatment-naïve patients only, 22 studies (N=17,010); treatment-experienced patients only, 12 studies (N=4,009); and both treatment-naïve and experienced patients, 9 studies (N=1,721). The pooled odds ratio for optimal adherence compared to suboptimal adherence for virologic failure for treatment-experienced patients was the highest; however, no statistically significant difference in pooled odds ratio was found between the three groups.

The relationship between adherence and virologic outcomes varied with type of adherence measurement. The pooled odds ratio for the self-report adherence measure (0.45; 95% CI: 0.37-0.55, I^2=31%) was higher than the pooled odds ratio for the pharmacy refill (0.29; 95% CI: 0.20-0.41, I^2=94%). The group using MEMS adherence measure had the lowest pooled odd ratio (0.15; 95% CI: 0.06-0.37, I^2=35%) for optimal adherence compared to suboptimal adherence for virologic failure. There was a trend towards significant difference across the odds of virologic failure between self-report and MEMS (regression coefficient -1.00; 95% CI: -2.05, 0.06, p=0.06), but not between self-report and pharmacy refill (regression coefficient -0.22; 95% CI: -0.78, 0.34, p=0.45).

The pooled odds ratios were also estimated by grouping studies using cut-off points for optimal adherence - studies with a cut-off point between 98% and 100%, 7 studies (N=3,940); studies with a cut-off point of ≥95%, 30 studies (N=17,779); and studies with a cut-off point of 80-90%, 6 studies (N=1,021). The pooled odds ratios for virologic

failure for optimal adherence compared to suboptimal adherence for each cut-off point were similar, with no statistically significant differences.

The pooled odds ratio for optimal adherence compared to suboptimal adherence for observational studies was significantly greater than randomised controlled studies (regression coefficient, 0.66; 95% CI: 0.10, 1.21, p=0.02). Studies were aggregated into three subgroups according to HIV-medication regimens: NNRTI-based, boosted PI-based, and unboosted PI-based. The pooled odds ratio for virologic failure for optimal adherence compared to suboptimal adherence for patients taking NNRTI-containing regimens was the highest, but the differences in pooled odds ratios between the regimens were not statistically significant.

Studies were subgrouped into two groups based on the HDI of the country in which the study was performed: very high HDI, 21 studies (N=10,466); low HDI, 19 studies (N=9,945). The pooled odds ratio for optimal adherence compared to suboptimal adherence for countries with low HDI (0.50; 95% CI: 0.35-0.72) was significantly higher than countries with very high HDI (0.23; 95% CI: 0.15-0.33).

A multivariate meta-regression model was built-in to examine the specific moderators of the between-study heterogeneity, including the following: study region, threshold used to define virologic failure, adherence measurement, study design and year of publication. Study design (observational study versus randomised controlled trials; regression coefficient 0.74, 95% CI: 0.04 - 1.43, $p<0.05$) and study region (developed versus developing countries; regression coefficient 0.56, 95% CI: 0.01-1.12, $p<0.05$) remained as independent predictors of between-study heterogeneity.

Table 15. Subgroup analysis adherence to antiretroviral therapy and virologic failure.

Analysis group	No of studies	Pooled odds ratio (95% CI)	Tests for heterogeneity	
			P value (Q statistic)	I^2 (%)
Study design:				
Randomised controlled trial	11	0.55 (0.33-0.92)	<0.001	85
Observational study	32	0.29 (0.22-0.38)	<0.001	90
HDI rank:				
High HDI	21	0.23 (0.15-0.33)	<0.001	91
Low HDI	19	0.50 (0.35-0.72)	<0.001	87
Regimen:				
NNRTI-based	17	0.54 (0.38-0.77)	<0.001	88
Boosted PI-based	4	0.31 (0.14-0.71)	0.06	59
Unboosted PI-based	5	0.25 (0.13-0.47)	0.11	47
Treatment experience:				
Naïve	22	0.33 (0.23-0.47)	<0.001	94
Experienced	12	0.52 (0.41-0.66)	0.36	9
Naïve and experienced	9	0.28 (0.17-0.46)	0.001	69
Threshold used to define virological failure:				
≤100 copies/mL	11	0.55 (0.41-0.74)	0.01	56
100-400 copies/mL	17	0.37 (0.26-0.54)	<0.001	88
≥500 copies/mL	14	0.25 (0.16-0.41)	<0.001	92

Analysis group	No of studies	Pooled odds ratio (95% CI)	Tests for heterogeneity P value (Q statistic)	I^2 (%)
Threshold used to define optimal adherence group:				
≥98-100%	7	0.54 (0.29-1.00)	<0.001	85
≥95%	30	0.34 (0.24-0.47)	<0.001	92
≥80-90%	6	0.34 (0.23-0.51)	0.57	0
Measurement:				
Self-report	14	0.45 (0.37-0.55)	0.13	31
Pharmacy refill	18	0.29 (0.20-0.41)	<0.001	94
MEMS	6	0.15 (0.06-0.37)	0.18	35
Pill count	4	0.80 (0.21-3.02)	<0.001	93

Table 16. Meta-regression analysis of moderators for the association between antiretroviral adherence and virologic failure.

Moderator	Category 1	Category 2	Regression coefficient (95%CI)	P-value	I^2 inconsistency Q statistic
Region	Developing countries	Developed countries	0.79 (0.25, 1.32)	0.004	89.2% 352.4 (38 df), p<0.001
Regimen	NNRTIs	Boosted PIs	0.58 (-0.42, 1.59)	0.257	88.8% 349.11 (39 df), p<0.001
Treatment experience	Experienced	Naïve	0.38 (-0.27, 1.04)	0.250	90.1% 404.22 (40 df), p<0.001
Threshold used to define virologic failure	100-400 copies/mL	≤100 copies/mL	-0.30 (-0.92, 0.33)	0.353	87.5% 312.53 (39 df), p<0.001
	≥500 copies/mL	≤100 copies/mL	-0.75 (-1.39, -0.12)	0.020	
Threshold used to define optimal adherence group	≥80-90%	≥98-100%	-0.56 (-1.62, -0.51)	0.304	90.7% 430.21 (40 df), p<0.001
	≥95%	≥98-100%	-0.54 (-1.31, 0.23)	0.171	
Measurement	Pharmacy refill	Self-report	-0.22 (-0.78, 0.34)	0.446	90.2% 398.75 (df 39), p<0.001
	MEMS	Self-report	-1.00 (-2.05, 0.06)	0.064	
	Pill count	Self-report	0.17 (-0.89, 1.24)	0.749	
Study design	RCT	Observational study	0.66 (0.10, 1.21)	0.020	88.7% 364.17 (41 df), p<0.001
Observation period	<=1 year	>1 year	0.15 (-0.38, 0.69)	0.574	90.1% 413.84 (31 df), p<0.001
Year of publication	≥2005	<2005	0.67 (0.07, 1.28)	0.028	89.6% 394.36 (41 df), p<0.001
Multivariate					

Moderator	Category 1	Category 2	Regression coefficient (95%CI)	P-value	I^2 inconsistency Q statistic
Region	Developing countries	Developed	0.56 (0.01, 1.12)	0.048	82.6% 172.5 (30 df), p<0.001
Threshold used to define virologic failure	≥500 copies/mL	≤100 copies/mL	-0.46 (-1.23, 0.30)	0.238	
Measurement	MEMS	Self-report	-0.50 (-1.58, 0.58)	0.366	
Study design	RCT	Observational study	0.74 (0.04, 1.43)	0.038	
Year of publication	≥2005	<2005	0.43 (-0.37, 1.23)	0.291	

7.6. Discussion

This meta-analysis of 43 studies, involving 27,905 participants, addresses a gap in the current HIV treatment adherence literature with a quantitative evaluation of the association between level of adherence and virologic outcomes among adults taking ART. This study revealed that adherence levels as low as 80-90% may be adequate for viral suppression in patients taking newer antiretroviral drugs. Our data also showed that pooled odds ratios for virologic failure for optimal adherence compared to suboptimal adherence were similar between NNRTI-based and boosted PI-based regimens. The effectiveness of newer antiretroviral agents at the lower level of adherence may encourage the prescribing of ART at an early stage of HIV infection.

The findings indicated that the mean proportion of patients who were reported to demonstrate optimal adherence worldwide was 63.4%, which is similar to a meta-analysis of 84 studies that reported 62% of patients take ≥90% of their prescribed ART

[47]. The results of this study demonstrate that adherence is robustly associated with virologic outcomes across the various types of adherence measure, ART regimen, study population, and reporting. The odds of virologic failure were almost three times higher for participants with suboptimal adherence compared with those with optimal adherence. This confirms that achieving long-term optimal adherence is indeed the Achilles' heel of successful virologic outcomes [371]. The need for clinicians to exert concerted efforts to maintain continuing optimal adherence to antiretroviral therapy is indisputable.

Classifying patients according to various optimal adherence thresholds (≥98-100%, ≥95%, and 80-90%) did not result in statistically significant differences in the odds of virologic failure. This finding is consistent with a meta-analysis of 37 studies in children that reported no significant group differences in virologic outcomes between different thresholds of good adherence [372]. This suggests that patients who achieved "perfect" (100%) or "near perfect" (≥95%) adherence did not necessarily have better virologic outcomes than patients who had achieved "good enough" (≥80-90%) adherence. This finding has clinical importance and is in line with previous studies [373, 374] that indicated that, while the need to maintain high levels of adherence to achieve long-term virologic suppression is clear, the level of adherence behaviour capable of sustaining viral suppression is broader than previously thought.

Considerable variation in the relationship between adherence and virologic outcomes was found based on the type of adherence measurement used in the studies we reviewed. For studies using self-reported adherence, the odds of virologic failure in participants with optimal adherence was about half that of participants with suboptimal adherence. The odds of virologic failure for optimal adherence were about one-third

and one-seventh that of the participants with suboptimal adherence using pharmacy refill and MEMS, respectively. Our meta-analysis undermines the validity of using self-reported adherence to distinguish virologic outcomes. A high proportion of patients with optimal self-reported adherence experienced virologic failure. Self-reported adherence is potentially confounded by social desirability and recall bias, which leads patients to over-estimate their actual adherence; [96] this method is inferior to MEMS in its ability to explain virologic outcomes.

Despite the findings [217, 218] of previous studies suggesting the need for different levels of optimal adherence between antiretroviral regimens for achieving similar virologic outcomes, classifying patients based on regimen did not result in statistically significant differences in the odds of virologic outcomes in this meta-analysis.

Pooled odds ratio for optimal adherence compared to suboptimal adherence for virologic failure for studies with virologic failure cut-offs <100 copies/mL were significantly higher than studies with virologic failure cut-offs between 500 copies/mL and 1000 copies/mL. The rate of virologic failure detected in patients with good adherence increased when studies defined a virologic failure at a low level of HIV-1 ribonucleic acid (RNA). The relationship between adherence and viral load improved when the level of detection of HIV-1 RNA increased. The tighter the definition of virologic failure the more likely it is to unmask suboptimal adherence.

The odds of virologic failure for optimal adherence were about half and one-third that of the patients with suboptimal adherence in countries with a low HDI and high HDI, respectively. More patients with optimal adherence experienced virologic failure in countries with low HDI than in countries with high HDI. This review indicates that patients with equal or better levels of optimal adherence in developing countries

compared to developed countries [113] does not necessarily translate into better virologic outcomes. This might be associated with the increase in pre-treatment antiretroviral drug resistance [375] and unavailability of baseline HIV drug resistance testing before initiation of ART [33] in resource-limited settings that have a potential to contribute to the increasing rates of virologic failure in optimally adherent patients. We support moves toward the use viral load monitoring at the point of care in resource-limited settings [376] to improve treatment outcomes.

Study design (observational study versus randomised controlled trials) was an independent predictor of between-study heterogeneity. More patients with optimal adherence experienced virologic failure in randomised controlled trials than in observational studies. Differences in estimated magnitude of treatment effect are very common between randomised controlled trials and observational studies [377]. This difference in virologic outcomes between study designs might be related with selection bias in observational studies [378] and higher quality and rigour of randomised controlled trials.

This meta-analysis shares the limitations intrinsic to meta-analysis in general and with studies of adherence in particular. We only included studies published in English, so we may have missed studies that were relevant to our research question during the literature search. When the included studies were stratified and analysed based on regimen, virologic failure cut-off, adherence cut-off and type of adherence measurement, heterogeneity between-studies remained high for most of the subgroups. Because of this high degree of heterogeneity, which was not entirely described either by subgroup analysis or by meta-regression, our pooled results need to be viewed with caution.

7.7. Conclusion

Irrespective of the cut-off point for optimal adherence, our findings support the tenet that optimal adherence to ART is associated with positive clinical outcomes. The threshold for optimal adherence to achieve better virologic outcomes appears to be wider than the commonly used cut-off point (≥95% adherence). Though patients taking ART should be instructed to attain ≥95% adherence, apprehensions of slightly lower adherence should not deter prescribing ART regimens at an early stage of HIV infection.

CHAPTER EIGHT

8. GENERAL DISCUSSION AND CONCLUSION

This body of work represents a significant step forward for Ethiopian research into HIV/AIDS and ART. Adherence to ART is a complex issue and understanding of its barriers and facilitators requires a comprehensive and holistic approach. We used a one-year prospective study and qualitative study to assess the association between adherence and a broad range of factors in adult HIV/AIDS patients. Adherence was measured using multiple adherence measures, which were evaluated with surrogate endpoints. A meta-analysis was performed to critically assess the association between optimal adherence to ART and virologic outcomes. ADRs associated with ART pose a unique challenge in the treatment of HIV/AIDS. We have assessed ADRs and their impact on treatment outcomes. We believe findings from this study have a number of implications for future research, clinical practice, and policy.

In this study, we found data in support of the following practical and methodological concerns. As there is no 'gold standard' measure of adherence [91], we not only used multiple measures of adherence but also validated these tests with a surrogate marker. A significant CD4 increase in adherent patients compared to non-adherent patients was found using the ACTG self-reported adherence measure. In this study, self-reported adherence differentiated meaningful patterns of adherence behaviour over other methods clinically, which is similar to the conclusion of a meta-analysis reported by Nieuwkerk et al. [379]. This finding supports the use of self-report of adherence in research and clinical practice in resource-limited settings.

Optimal adherence in this study was defined as achieving 95% or more of self-reported dose and time adherence. The meta-analysis data highlighted classifying patients according to various optimal adherence thresholds (>90-100%, ≥95%, and 80-90%) did not result in statistically significant differences in the odds of virologic failure. Viswanathan *et al*. [374] found that odds of virologic suppression did not differ for 85%-89% adherence compared to those with ≥95% adherence in patients taking NNRT-containing regimens. While all patients taking ART should be trained to achieve ≥95% adherence, apprehension about slightly lower adherence should not hamper prescribing ART at an early stage.

Adherence to ART is a dynamic behaviour. The prospective nature of this study allowed assessment of changing adherence levels over time. The proportion of non-adherent patient increased over the study period, as reported elsewhere [231, 380]. Based on ACTG self-reported adherence that combined dose and time adherence, 23.4% of patients were non-adherent at 12 months, which is similar to the combined dose and time adherence reported by Amberbir et al. [151] at 3 months, in Jimma, Ethiopia. A meta-analysis by Ortego *et al*. [47] reported that 33% of HIV/AIDS patients in sub-Saharan Africa studies were non-adherent, which is greater than the rate determined in this study. The difference in the rate of non-adherence among studies may be due to dissimilarity in study design and setting. In this study, the increase in non-adherent patients over the study period varied using different adherence measures; VAS better identified non-adherent patients. Researchers in resource-limited settings may choose VAS over other measures for this advantage.

We used a simultaneous methodological triangulation approach to gain a comprehensive understanding of the problem of ART adherence. Data were obtained

from the various sources (i.e. patients taking ART, case managers, and nurses) and different techniques of data collection (i.e. semi-structured interviews, focus group discussion, clinical records, and a follow-up survey) were applied. This methodological triangulation has resulted in more valid and reliable findings. This study has confirmed the importance of mixed methods and encourages researchers to use this approach to examine multifaceted issues.

Cultural suitability was cautiously considered in the design and execution of the prospective study and exploratory qualitative study. Forward and backward translation and pretesting was carried out to ensure the validity and reliability of questionnaires. Only emerging concepts and categories obtained from analyses of the interviews and focus groups using Amharic were subsequently translated into English. Undertaking a translation after completing the data analyses in the original language decreased cost, preserved meaning, and improved the validity of the data [381].The authors suggest that translation after completing the data analysis in the original language improved the quality of findings.

The qualitative data highlighted socio-economic constraints, such as unemployment and food insecurity, as barriers to adherence and retention in HIV care. HIV treatment knowledge score and attaining secondary education or above were significantly associated with adherence in the bivariate analysis. The impacts of socio-economic constraints were also indirectly supported by our prospective study, in which a lower body mass index (BMI) at baseline was independently associated with non-adherence. Besides, being unemployed was an independent predictor of experiencing severe ADRs, which were more likely in non-adherent patients. As financial insecurity is a major problem in resource-limited settings, including Ethiopia [382], improving food security

and job opportunities in patients taking ART may improve adherence to ART and treatment outcomes. Further studies are needed to evaluate the effect of such interventions on adherence to ART among economically disadvantaged adults who are initiated on ART in Ethiopia.

In the qualitative study, psychosocial factors such as stigma and discrimination and religious rituals (e.g. being baptised with holy water, fasting) were found as important barriers to adherence. Significant associations were reported between adherence and psychological variables such as stigma and discrimination, depression, and belief about medicines in the univariate analysis, but these associations did not persist in the multivariate analysis. A systematic review by Sweeney et al. [383] confirmed that stigma was negatively associated with adherence to HIV-medication. Tackling stigma and discrimination might also improve patients' abilities to adhere to ART and continue attending HIV care in Ethiopia.

Social support and use of reminders were identified as important facilitators of adherence in the qualitative study. In the prospective study, the use of electronic reminder devices was independently associated with medication adherence. The use of mobile phone text messaging to improve adherence was also confirmed in randomised clinical trials [155, 156] carried out in resource-limited settings. Given that the majority of patients in this study possessed a mobile phone, and were able to send and receive text messages, more rigorous randomised controlled trials are warranted using mobile phones to improve patients' adherence to ART.

Antiretrovirals are the most commonly reported class of pharmacological agents implicated in ADRs in Africa based on the WHO global Individual Case Safety (ICSR) database [384]. ADRs reporting into ICSR database from Ethiopia is extremely low

compared to other African countries such as South Africa and Morocco [384]. This study evaluated the burden of ADRs of antiretrovirals and their impact on treatment outcomes. In our follow-up study, we found that more than one-third of patients who were initiated on ART experienced severe ADRs. Shet et al. [263] reported that 26.5% of patients who were initiated on ART experienced at least one severe reaction over a two-year study period. The high incidence of severe ADRs in this study might be related to rigorous prospective data collection, which helped to detect ADRs that might be unreported in other studies. The majority of severe ADRs were reported within the first three months. Patients who experienced severe ADRs were significantly less likely to be adherent, as described elsewhere [6, 7]. Dose omission or treatment discontinuations in order to avoid intolerable side effects were detected in our qualitative study. A high distress score as the result of HIV symptoms and ADRs was independently related to non-adherence. To our knowledge, this is the first study to demonstrate the negative impact of distress due to antiretroviral drug ADRs on adherence. Distress causes undesirable health behaviour [239] that may impair patients from attaining optimal adherence to ART.

The most important class of severe ADRs were gastrointestinal complaints, followed by cutaneous reactions and haematological abnormalities, similar to the reactions reported in the ICSR database [384]. A systematic review and meta-analysis by Al-Dakkak et al. [385] reported that patients who experienced ART ADRs were less likely to be adherent. Almost half of the severe ADRs related to ART were found to be preventable, highlighting the importance of improving ADR monitoring practices to improve ART adherence and retention in HIV care. Strategies for monitoring ADRs associated with ART are diverse [62]. Future research needs to focus on rationalising ART ADR

monitoring [385]. Policymakers need to consider balancing the risks of severe ADRs associated with the continuing use of older antiretroviral drugs such as zidovudine over the cost of newer antiretroviral agents with a better ADR profile.

Scale-up of treatment and care for patients with HIV/AIDS in Ethiopia has been a significant clinical success. The full advantage of the scale-up cannot be recognised without attaining long-term optimal adherence and retention in care. This study has identified several factors that influence long-term adherence to ART and contributed in the arena of HIV/AIDS treatment and care in Ethiopia in a number of ways. Implementation of measures to consistently monitor ADRs, improving job and food security, and promoting the use of reminder devices may improve adherence and treatment outcomes in Ethiopian patients initiated on ART.

Recommendations and Future Directions

- Several issues for future research arose from this work. A number of factors (such as disclosure of HIV status, stigma and discrimination, depression, and social support) that are reported as strong predictors elsewhere [224], as well as some other factors identified in our qualitative study, were not identified as independent significant predictors of measured adherence in the prospective study. Adherence is a multifaceted issue; no study can evaluate all variables potentially related to ART. Future research aimed to examine these and some other factors (e.g. partner violence) using a larger sample size and a longer follow-up is required.
- This work has identified important factors including food security, ADRs, and use of reminder devices that influence long-term adherence and retention in HIV care using a mixed methods approach in the Ethiopian setting. However, the impact of these factors on treatment outcomes might be subjected to potential bias. Thus, it

would be worthwhile to evaluate the influence of these factors using randomised controlled trials to obtain sound evidence before implementing these findings in clinical practice.

- Clinical monitoring with biannual CD4 counts is used to routinely monitor treatment response for patients taking ART in Ethiopia. Self-reported adherence predicted CD4 changes in patients initiated on ART in this study. The changes in CD4 count tend to occur later and are, consequently, less visible than the changes in HIV viral load [247]. Adherence values have greater accuracy in detecting virologic changes [386]. Future studies need to validate adherence measures with virologic outcomes in the Ethiopian setting.
- Self-reported adherence measures have several advantages and are widely applied in research and clinical settings [93]. In this study, self-reported adherence measures (ACTG self-report and VAS) better identified non-adherent patients and predicted clinical outcomes. Future studies in resource-limited settings may choose VAS and ACTG self-reported adherence measures for these advantages.
- One-third of patients initiated on ART experienced severe ADRs within a one-year period and these events were related to worse treatment outcomes. Severe laboratory ADRs were underreported in our study as a result of inadequate number of laboratory testing being performed to monitor ADRs in these resource-limited hospitals. Future studies should focus on performing a broad range laboratory tests to examine the full impact of ADRs on treatment outcomes. Besides, future studies may address interventions to improve the detection of ADRs in patients initiated ART.

References

1. *Pneumocystis pneumonia--Los Angeles.* MMWR Morb Mortal Wkly Rep, 1981. **30**(21): p. 250-2.
2. Simon, V., D.D. Ho, and Q. Abdool Karim, *HIV/AIDS epidemiology, pathogenesis, prevention, and treatment.* The Lancet, 2006. **368**(9534): p. 489-504.
3. Weinberg, J.L. and C.L. Kovarik, *The WHO clinical staging system for HIV/AIDS.* Virtual Mentor, 2010. **12**(3): p. 202-6.
4. Chaisson, R.E., et al., *Impact of opportunistic disease on survival in patients with HIV infection.* AIDS, 1998. **12**(1): p. 29-33.
5. UNAIDS, *How AIDS changed every thing-MDG6: 15 years, 15 lessons of hope from the AIDS response*. 2015, UNAIDS: Geneva, Switzerland
6. Haase, A.T., *Targeting early infection to prevent HIV-1 mucosal transmission.* Nature, 2010. **464**(7286): p. 217-223.
7. Gouws, E., et al., *Short term estimates of adult HIV incidence by mode of transmission: Kenya and Thailand as examples.* Sex Transm Infect, 2006. **82 Suppl 3**: p. iii51-55.
8. Grewe, C., A. Beck, and H.R. Gelderblom, *HIV: early virus-cell interactions.* J Acquir Immune Defic Syndr, 1990. **3**(10): p. 965-74.
9. Stein, B.S. and E.G. Engleman, *Intracellular processing of the gp160 HIV-1 envelope precursor. Endoproteolytic cleavage occurs in a cis or medial compartment of the Golgi complex.* J Biol Chem, 1990. **265**(5): p. 2640-9.
10. Pancera, M., et al., *Structure of HIV-1 gp120 with gp41-interactive region reveals layered envelope architecture and basis of conformational mobility.* Proc Natl Acad Sci U S A, 2010. **107**(3): p. 1166-71.
11. Kwong, P.D., et al., *Structure of an HIV gp 120 envelope glycoprotein in complex with the CD4 receptor and a neutralizing human antibody.* Nature, 1998: p. 648-659.

12. Center, R.J., et al., *Oligomeric structure of the human immunodeficiency virus type 1 envelope protein on the virion surface.* J. Virol, 2002. **76**(15): p. 7863-7867.

13. Doms, R.W., *Fusing HIV and chemokine receptors.* J Immunol, 2011. **186**(11): p. 6073-5.

14. Qui, S., et al., *The binding mode of fusion inhibitor T20 onto HIV-1 gp41 p41 and relevant T20-resistant mechanisms explored by computational study.* Curr HIV Res., 2012. **10**(2): p. 182-94.

15. Berkhout, B., D. Eggink, and R.W. Sanders, *Is there a future for antiviral fusion inhibitors?* Curr Opin Virol., 2012. **2**(1): p. 50-59.

16. Götte, M., X. Li, and M.A. Wainberg, *HIV-1 reverse transcription: A brief overview focused on structure-function relationships among molecules involved in initiation of the reaction.* Arch. Biochem. Biophys., 1999. **365**(2): p. 199-210.

17. Wu, Y., *HIV-1 gene expression: lessons from provirus and non-integrated DNA.* Retrovirology, 2004. **1**(1): p. 13.

18. Briggs, J.A. and H.G. Krausslich, *The molecular architecture of HIV.* J Mol Biol, 2011. **410**(4): p. 491-500.

19. Farnet, C.M. and F.D. Bushman, *HIV cDNA integration: molecular biology and inhibitor development.* AIDS, 1996. **10**: p. 3-12.

20. Engelman, A. and P. Cherepanov, *The structural biology of HIV-1: mechanistic and therapeutic insights.* Nat Rev Microbiol, 2012. **10**(4): p. 279-90.

21. Panel on Antiretroviral Guidelines for Adults and Adolescents, *Guidelines for the use of antiretroviral agents in HIV-1-infected adults and adolescents*. 2015, US Department of Health and Human Services.

22. Greene, W.C. and B.M. Peterlin, *Charting HIV's remarkable voyage through the cell: Basic science as a passport to future therapy.* Nat Med, 2002. **8**(7): p. 673-80.

23. Frankel, A.D. and J.A. Young, *HIV-1: fifteen proteins and an RNA.* Annu Rev Biochem, 1998. **67**: p. 1-25.

24. Sakuragi, J., *Morphogenesis of the Infectious HIV-1 Virion.* Front Microbiol, 2011. **2**: p. 242.

25. Maartens, G., C. Celum, and S.R. Lewin, *HIV infection: epidemiology, pathogenesis, treatment, and prevention.* Lancet, 2014. **384**(9939): p. 258-71.

26. Volberding, P.A. and S.G. Deeks, *Antiretroviral therapy and management of HIV infection.* Lancet, 2010. **376**(9734): p. 49-62.

27. WHO, *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendation for a public health approach*. 2013: Geneva, Switzerland

28. Fischl, M.A., et al., *The efficacy of azidothymidine (AZT) in the treatment of patients with AIDS and AIDS-related complex. A double-blind, placebo-controlled trial.* N Engl J Med, 1987. **317**(4): p. 185-91.

29. Pau, A.K. and J.M. George, *Antiretroviral therapy: current drugs.* Infect Dis Clin North Am, 2014. **28**(3): p. 371-402.

30. Marrazzo, J.M., et al., *HIV prevention in clinical care settings: 2014 recommendations of the International Antiviral Society-USA Panel.* JAMA, 2014. **312**(4): p. 390-409.

31. Piliero, P.J., *Pharmacokinetic properties of nucleoside/nucleotide reverse transcriptase inhibitors.* J Acquir Immune Defic Syndr, 2004. **37 Suppl 1**: p. S2-S12.

32. Back, D.J., et al., *The pharmacology of antiretroviral nucleoside and nucleotide reverse transcriptase inhibitors: implications for once-daily dosing.* J Acquir Immune Defic Syndr, 2005. **39 Suppl 1**: p. S1-23, quiz S24-25.

33. Gunthard, H.F., et al., *Antiretroviral treatment of adult HIV infection: 2014 recommendations of the International Antiviral Society-USA Panel.* JAMA, 2014. **312**(4): p. 410-25.

34. Smith, P.F., R. DiCenzo, and G.D. Morse, *Clinical pharmacokinetics of non-nucleoside reverse transcriptase inhibitors.* Clin Pharmacokinet, 2001. **40**(12): p. 893-905.

35. Kobin, A.B. and N.U. Sheth, *Levels of adherence required for virologic suppression among newer antiretroviral medications.* Ann Pharmacother, 2011. **45**(3): p. 372-9.

36. UNAIDS, *90-90-90: An ambitious treatment target to help end the AIDS epidemic*. 2014, UNAIDS: Geneva, Switzerland.

37. UNAIDS, *UNAIDS World AIDS day report*. 2011: Geneva, Switzerland.

38. Schwarcz, L., et al., *Declining incidence of AIDS-defining opportunistic illnesses: Results from 16 years of population-based AIDS surveillance.* AIDS, 2013. **27**(4): p. 597-605.

39. Reniers, G., et al., *Mortality trends in the era of antiretroviral therapy: Evidence from the network for analysing longitudinal population based HIV/AIDS data on Africa (ALPHA).* AIDS, 2014. **28 Suppl 4**: p. S533-42.

40. Severe, P., et al., *Early versus standard antiretroviral therapy for HIV-infected adults in Haiti.* N Engl J Med, 2010. **363**(3): p. 257-265.

41. Sterne, J.A., et al., *Timing of initiation of antiretroviral therapy in AIDS-free HIV-1-infected patients: A collaborative analysis of 18 HIV cohort studies.* Lancet, 2009. **373**(9672): p. 1352-63.

42. Townsend, C.L., et al., *Low rates of mother-to-child transmission of HIV following effective pregnancy interventions in the United Kingdom and Ireland, 2000-2006.* AIDS, 2008. **22**(8): p. 973-81.

43. Cohen, M.S., et al., *Prevention of HIV-1 infection with early antiretroviral therapy.* N Engl J Med, 2011. **365**(6): p. 493-505.

44. Hawkins, T., *Understanding and managing the adverse effects of antiretroviral therapy.* Antiviral Res, 2010. **85**(1): p. 201-9.

45. Bezabhe, W.M., et al., *Adverse drug reactions and clinical outcomes in patients initiated on antiretroviral therapy: A prospective cohort study from Ethiopia.* Drug Saf, 2015. **38**(7): p. 629-39.

46. Fumaz, C.R., et al., *Long-term neuropsychiatric disorders on efavirenz-based approaches: quality of life, psychologic issues, and adherence.* J Acquir Immune Defic Syndr, 2005. **38**(5): p. 560-5.

47. Ortego, C., et al., *Adherence to highly active antiretroviral therapy (HAART): a meta-analysis.* AIDS Behav, 2011. **15**(7): p. 1381-96.

48. d'Arminio Monforte, A., et al., *Insights into the reasons for discontinuation of the first highly active antiretroviral therapy (HAART) regimen in a cohort of antiretroviral naive patients. I.CO.N.A. Study Group. Italian cohort of antiretroviral-naive patients.* AIDS, 2000. **14**(5): p. 499-507.

49. Hill, A. and A. Balkin, *Risk factors for gastrointestinal adverse events in HIV treated and untreated patients.* AIDS Rev, 2009. **11**(1): p. 30-8.

50. Boyle, A., et al., *An investigation into frequency and reasons why patients switch antiretroviral therapy and which antiretrovirals are commonly implicated in toxicity.* J Int AIDS Soc, 2012. **15**(6): p. 18121.

51. Markowitz, M., et al., *A preliminary study of ritonavir, an inhibitor of HIV-1 protease, to treat HIV-1 infection.* N Engl J Med, 1995. **333**(23): p. 1534-9.

52. Malan, N., et al., *Gastrointestinal tolerability and quality of life in antiretroviral-naive HIV-1-infected patients: data from the CASTLE study.* AIDS care, 2010. **22**(6): p. 677-86.

53. Molina, J.M., et al., *Once-daily atazanavir/ritonavir compared with twice-daily lopinavir/ritonavir, each in combination with tenofovir and emtricitabine, for management of antiretroviral-naive HIV-1-infected patients: 96-week efficacy and safety results of the CASTLE study.* J Acquir Immune Defic Syndr, 2010. **53**(3): p. 323-32.

54. Ortiz, R., et al., *Efficacy and safety of once-daily darunavir/ritonavir versus lopinavir/ritonavir in treatment-naive HIV-1-infected patients at week 48.* AIDS, 2008. **22**(12): p. 1389-97.

55. Elgadi, M.M. and P.J. Piliero, *Boosted tipranavir versus darunavir in treatment-experienced patients: observational data from the randomized POTENT trial.* Drugs R D, 2011. **11**(4): p. 295-302.

56. DeJesus, E., et al., *Abacavir versus zidovudine combined with lamivudine and efavirenz, for the treatment of antiretroviral-naive HIV-infected adults.* Clin Infect Dis, 2004. **39**(7): p. 1038-46.

57. Gallant, J.E., et al., *Tenofovir DF, emtricitabine, and efavirenz vs. zidovudine, lamivudine, and efavirenz for HIV.* N Engl J Med, 2006. **354**(3): p. 251-60.

58. DeJesus, E., et al., *Impact of switching virologically suppressed, HIV-1-infected patients from twice-daily fixed-dose zidovudine/lamivudine to once-daily fixed-dose tenofovir disoproxil fumarate/emtricitabine.* HIV Clin Trials, 2008. **9**(2): p. 103-14.

59. van Leth, F., et al., *Nevirapine and efavirenz elicit different changes in lipid profiles in antiretroviral-therapy-naive patients infected with HIV-1.* PLoS Med, 2004. **1**(1): p. e19.

60. Hodder, S., et al., *Effect of gender and race on the week 48 findings in treatment-naive, HIV-1-infected patients enrolled in the randomized, phase III trials ECHO and THRIVE.* HIV Med, 2012. **13**(7): p. 406-15.

61. Staszewski, S., et al., *Efavirenz plus zidovudine and lamivudine, efavirenz plus indinavir, and indinavir plus zidovudine and lamivudine in the treatment of HIV-1 infection in adults. Study 006 Team.* N Engl J Med, 1999. **341**(25): p. 1865-73.

62. Shubber, Z., et al., *Adverse events associated with nevirapine and efavirenz-based first-line antiretroviral therapy: a systematic review and meta-analysis.* AIDS, 2013. **27**(9): p. 1403-12.

63. Arendt, G., et al., *Neuropsychiatric side effects of efavirenz therapy.* Expert Opin Drug Saf, 2007. **6**(2): p. 147-54.

64. Gutierrez, F., et al., *Prediction of neuropsychiatric adverse events associated with long-term efavirenz therapy, using plasma drug level monitoring.* Clin Infect Dis, 2005. **41**(11): p. 1648-53.

65. Munoz-Moreno, J.A., et al., *Neuropsychiatric symptoms associated with efavirenz: prevalence, correlates, and management. A neurobehavioral review.* AIDS Rev, 2009. **11**(2): p. 103-9.

66. Ward, D.J. and J.M. Curtin, *Switch from efavirenz to nevirapine associated with resolution of efavirenz-related neuropsychiatric adverse events and improvement in lipid profiles.* AIDS Patient Care STDS, 2006. **20**(8): p. 542-8.

67. Carr, A. and D.A. Cooper, *Adverse effects of antiretroviral therapy.* Lancet, 2000. **356**(9239): p. 1423-30.

68. Chaponda, M. and M. Pirmohamed, *Hypersensitivity reactions to HIV therapy.* British Journal of Clinical Pharmacology, 2011. **71**(5): p. 659-671.

69. Adkins, J.C. and S. Noble, *Efavirenz.* Drugs, 1998. **56**(6): p. 1055-64; discussion 1065-6.

70. Montessori, V., et al., *Adverse effects of antiretroviral therapy for HIV infection.* CMAJ, 2004. **170**(2): p. 229-38.

71. Ananworanich, J., et al., *Incidence and risk factors for rash in Thai patients randomized to regimens with nevirapine, efavirenz or both drugs.* AIDS, 2005. **19**(2): p. 185-92.

72. Stern, J.O., et al., *A comprehensive hepatic safety analysis of nevirapine in different populations of HIV infected patients.* J Acquir Immune Defic Syndr, 2003. **34 Suppl 1**: p. S21-33.

73. Murphy, R.L., *Defining the toxicity profile of nevirapine and other antiretroviral drugs.* J Acquir Immune Defic Syndr, 2003. **34 Suppl 1**: p. S15-20.

74. Parker, S.R., *The skin and HIV: no superficial matter.* Top Antivir Med, 2014. **22**(4): p. 680-4.

75. Moyle, G., et al., *Changes in hematologic parameters and efficacy of thymidine analogue-based, highly active antiretroviral therapy: a meta-analysis of six prospective, randomized, comparative studies.* Clin Ther, 2004. **26**(1): p. 92-7.

76. Rachlis, A. and M.M. Fanning, *Zidovudine toxicity. Clinical features and management.* Drug Saf, 1993. **8**(4): p. 312-20.

77. Max, B. and R. Sherer, *Management of the adverse effects of antiretroviral therapy and medication adherence.* Clin Infect Dis, 2000. **30 Suppl 2**: p. S96-116.

78. Subbaraman, R., et al., *Adverse effects of highly active antiretroviral therapy in developing countries.* Clin Infect Dis, 2007. **45**(8): p. 1093-101.

79. Firnhaber, C., et al., *Comparisons of anemia, thrombocytopenia, and neutropenia at initiation of HIV antiretroviral therapy in Africa, Asia, and the Americas.* Int J Infect Dis, 2010. **14**(12): p. e1088-92.

80. Martí-Carvajal, A.J., et al., *Treatment for anemia in people with AIDS.* Cochrane Database Syst Rev, 2011(10): p. 1-61.

81. Ssali, F., et al., *Prevalence, incidence and predictors of severe anaemia with zidovudine-containing regimens in African adults with HIV infection within the DART trial.* Antivir Ther, 2006. **11**(6): p. 741-9.

82. van Hensbroek, M.B., F. Jonker, and I. Bates, *Severe acquired anaemia in Africa: new concepts.* Br J Haematol, 2011. **156**(6): p. 690-695.

83. Drain, P.K., et al., *Micronutrients in HIV-positive persons receiving highly active antiretroviral therapy.* The American journal of clinical nutrition, 2007. **85**(2): p. 333-345.

84. Kreuzer, K.A. and J. Rockstroh, *Pathogenesis and pathophysiology of anemia in HIV infection.* Annals of hematology, 1997. **75**(5): p. 179-187.

85. Sawyer, S.M. and R.A. Aroni, *Sticky issue of adherence.* J Paediatr Child Health, 2003. **39**(1): p. 2-5.

86. Sabaté, E., *Adherence to long-term therapies: evidence for action*. 2003, World Health Organization: Geneva.

87. Osterberg, L. and T. Blaschke, *Adherence to medication.* N Engl J Med, 2005. **353**(5): p. 487-497.

88. Cramer, J.A., et al., *Medication compliance and persistence: terminology and definitions.* Value Health, 2008. **11**(1): p. 44-7.

89. Paterson, D.L., et al., *Adherence to protease inhibitor therapy and outcomes in patients with HIV infection.* Ann Intern Med, 2000. **133**(1): p. 21-30.

90. Chesney, M.A., et al., *Self-reported adherence to antiretroviral medications among participants in HIV clinical trials: the AACTG adherence instruments.* AIDS care, 2000. **12**(3): p. 255-266.

91. Paterson, D.L., B. Potoski, and B. Capitano, *Measurement of adherence to antiretroviral medications.* J Acquir Immune Defic Syndr, 2002. **31**: p. S103.

92. Simoni, J.M., et al., *Self-report measures of antiretroviral therapy adherence: A review with recommendations for HIV research and clinical management.* AIDS Behav, 2006. **10**(3): p. 227-45.

93. Miller, L.G. and R.D. Hays, *Measuring adherence to antiretroviral medications in clinical trials.* HIV Clin Trials, 2000. **1**(1): p. 36-46.

94. Reynolds, N.R., et al., *Optimizing measurement of self-reported adherence with the ACTG Adherence Questionnaire: a cross-protocol analysis.* J Acquir Immune Defic Syndr, 2007. **46**(4): p. 402-9.

95. Wagner, G.J. and J.G. Rabkin, *Measuring medication adherence: are missed doses reported more accurately then perfect adherence?* AIDS care, 2000. **12**(4): p. 405-8.

96. Wagner, G. and L.G. Miller, *Is the influence of social desirability on patients' self-reported adherence overrated?* J Acquir Immune Defic Syndr, 2004. **35**(2): p. 203-4.

97. Lu, M., et al., *Optimal recall period and response task for self-reported HIV medication adherence.* AIDS and Behav, 2008. **12**(1): p. 86-94.

98. Farmer, K.C., *Methods for measuring and monitoring medication regimen adherence in clinical trials and clinical practice.* Clin Ther, 1999. **21**(6): p. 1074-90.

99. Kerr, T., et al., *Measuring adherence to highly active antiretroviral therapy: implications for research and practice.* Curr HIV/AIDS Rep, 2005. **2**(4): p. 200-5.

100. Gutierrez, E.B., et al., *Measuring Adherence to Antiretroviral Treatment: The Role of Pharmacy Records of Drug Withdrawals.* AIDS Behav, 2012. **16**(6): p. 1482-1490.

101. Ross-Degnan, D., et al., *Measuring adherence to antiretroviral treatment in resource-poor settings: the clinical validity of key indicators.* BMC Health Serv Res, 2010. **10**: p. 42.

102. Berg, K.M. and J.H. Arnsten, *Practical and conceptual challenges in measuring antiretroviral adherence.* Journal of acquired immune deficiency syndromes (1999), 2006. **43**(Suppl 1): p. S79.

103. Fairley, C.K., A. Permana, and T.R. Read, *Long-term utility of measuring adherence by self-report compared with pharmacy record in a routine clinic setting.* HIV Med, 2005. **6**(5): p. 366-9.

104. Townsend, M.L., et al., *Association between pharmacy medication refill-based adherence rates and cd4 count and viral-load responses: A retrospective analysis in treatment-experienced adults with HIV.* Clin Ther, 2007. **29**(4): p. 711-6.

105. Pearson, C.R., et al., *Assessing antiretroviral adherence via electronic drug monitoring and self-report: an examination of key methodological issues.* AIDS Behav, 2007. **11**(2): p. 161-73.

106. Sabin, L.L., et al., *Using electronic drug monitor feedback to improve adherence to antiretroviral therapy among HIV-positive patients in China.* AIDS Behav, 2010. **14**(3): p. 580-589.

107. Lyimo, R.A., et al., *Measuring adherence to antiretroviral therapy in northern Tanzania: feasibility and acceptability of the Medication Event Monitoring System.* BMC Public Health, 2011. **11**: p. 92.

108. Haberer, J.E., et al., *Real-time adherence monitoring for HIV antiretroviral therapy.* AIDS Behav, 2010. **14**(6): p. 1340-6.

109. Podsadecki, T.J., et al., *"White coat compliance" limits the reliability of therapeutic drug monitoring in HIV-1-infected patients.* HIV Clin Trials, 2008. **9**(4): p. 238-46.

110. Owen, A. and S.H. Khoo, *Pharmacogenetics of antiretroviral agents.* Curr Opin HIV AIDS, 2008. **3**(3): p. 288-95.

111. Li, J., et al., *Worldwide variation in human drug-metabolism enzyme genes CYP2B6 and UGT2B7: implications for HIV/AIDS treatment.* Pharmacogenomics, 2012. **13**(5): p. 555-70.

112. Liu, X., Q. Ma, and F. Zhang, *Therapeutic drug monitoring in highly active antiretroviral therapy.* Expert Opinion on Drug Safety, 2010. **9**(5): p. 743-758.

113. Mills, E.J., et al., *Adherence to antiretroviral therapy in sub-Saharan Africa and North America: a meta-analysis.* JAMA, 2006. **296**(6): p. 679-90.

114. Chesney, M.A., *Factors affecting adherence to antiretroviral therapy.* Clin Infect Dis, 2000. **30 Suppl 2**: p. S171-6.

115. Alakija Kazeem, S., et al., *Factors influencing adherence to antiretroviral medication in Ilorin, Nigeria.* J Int Assoc Physicians AIDS Care (Chic), 2010. **9**(3): p. 191-5.

116. Maqutu, D., et al., *Determinants of optimal adherence over time to antiretroviral therapy amongst HIV positive adults in South Africa: a longitudinal study.* AIDS Behav, 2011. **15**(7): p. 1465-74.

117. Kamau, T.M., et al., *Coping self-efficacy as a predictor of adherence to antiretroviral therapy in men and women living with HIV in Kenya.* AIDS Patient Care STDS, 2011. **25**(9): p. 557-61.

118. Rougemont, M., et al., *Antiretroviral treatment adherence and its determinants in Sub-Saharan Africa: a prospective study at Yaounde Central Hospital, Cameroon.* AIDS research and therapy, 2009. **6**: p. 21.

119. Sasaki, Y., et al., *Adherence to antiretroviral therapy (ART) during the early months of treatment in rural Zambia: influence of demographic characteristics and social surroundings of patients.* Ann Clin Microbiol Antimicrob, 2012. **11**: p. 34.

120. Dewing, S., et al., *Predictors of poor adherence among people on antiretroviral treatment in Cape Town, South Africa: a case-control study.* AIDS care, 2015. **27**(3): p. 342-9.

121. Adewuya, A.O., et al., *The effect of psychological distress on medication adherence in persons with HIV infection in Nigeria.* Psychosomatics, 2010. **51**(1): p. 68-73.

122. Birbeck, G.L., et al., *Neuropsychiatric and socioeconomic status impact antiretroviral adherence and mortality in rural Zambia.* Am J Trop Med Hyg, 2011. **85**(4): p. 782-9.

123. Bell, D.J., et al., *Adherence to antiretroviral therapy in patients receiving free treatment from a government hospital in Blantyre, Malawi.* J Acquir Immune Defic Syndr, 2007. **45**(5): p. 560-3.

124. Do, N.T., et al., *Psychosocial factors affecting medication adherence among HIV-1 infected adults receiving combination antiretroviral therapy (cART) in Botswana.* AIDS Res Hum Retroviruses, 2010. **26**(6): p. 685-91.

125. Eholie, S.P., et al., *Field adherence to highly active antiretroviral therapy in HIV-infected adults in Abidjan, Cote d'Ivoire.* J Acquir Immune Defic Syndr, 2007. **45**(3): p. 355-8.

126. Elul, B., et al., *High levels of adherence and viral suppression in a nationally representative sample of HIV-infected adults on antiretroviral therapy for 6, 12 and 18 months in Rwanda.* PLoS One, 2013. **8**(1): p. e53586.

127. Etard, J.F., et al., *A 84-month follow up of adherence to HAART in a cohort of adult Senegalese patients.* Trop Med Int Health, 2007. **12**(10): p. 1191-8.

128. Diabate, S., M. Alary, and C.K. Koffi, *Determinants of adherence to highly active antiretroviral therapy among HIV-1-infected patients in Cote d'Ivoire.* AIDS, 2007. **21**(13): p. 1799-803.

129. Falang, K.D., P. Akubaka, and N.S. Jimam, *Patient factors impacting antiretroviral drug adherence in a Nigerian tertiary hospital.* J Pharmacol Pharmacother, 2012. **3**(2): p. 138-42.

130. Nozaki, I., et al., *Social factors affecting ART adherence in rural settings in Zambia.* AIDS care, 2011. **23**(7): p. 831-8.

131. Watt, M.H., et al., *Factors associated with self-reported adherence to antiretroviral therapy in a Tanzanian setting.* AIDS care, 2010. **22**(3): p. 381-9.

132. Orrell, C., et al., *Adherence is not a barrier to successful antiretroviral therapy in South Africa.* AIDS, 2003. **17**(9): p. 1369-75.

133. Jaquet, A., et al., *Alcohol use and non-adherence to antiretroviral therapy in HIV-infected patients in West Africa.* Addiction, 2010. **105**(8): p. 1416-21.

134. Oku, A.O., et al., *Prevalence and determinants of adherence to highly active antiretroviral therapy amongst people living with HIV/AIDS in a rural setting in south-south Nigeria.* Afr J Reprod Health, 2014. **18**(1): p. 133-43.

135. Unge, C., et al., *Long-term adherence to antiretroviral treatment and program drop-out in a high-risk urban setting in sub-Saharan Africa: a prospective cohort study.* PLoS One, 2010. **5**(10): p. e13613.

136. Weidle, P.J., et al., *Adherence to antiretroviral therapy in a home-based AIDS care programme in rural Uganda.* Lancet, 2006. **368**(9547): p. 1587-94.

137. Denison, J.A., et al., *Incomplete adherence among treatment-experienced adults on antiretroviral therapy in Tanzania, Uganda and Zambia.* AIDS, 2015. **29**(3): p. 361-71.

138. Munene, E. and B. Ekman, *Association between patient engagement in HIV care and antiretroviral therapy medication adherence: cross-sectional evidence from a regional HIV care center in Kenya.* AIDS care, 2015. **27**(3): p. 378-86.

139. Oyugi, J.H., et al., *Treatment interruptions predict resistance in HIV-positive individuals purchasing fixed-dose combination antiretroviral therapy in Kampala, Uganda.* AIDS, 2007. **21**(8): p. 965-71.

140. Pefura-Yone, E.W., et al., *Non-adherence to antiretroviral therapy in Yaounde: prevalence, determinants and the concordance of two screening criteria.* J Infect Public Health, 2013. **6**(4): p. 307-15.

141. Berhe, N., D. Tegabu, and M. Alemayehu, *Effect of nutritional factors on adherence to antiretroviral therapy among HIV-infected adults: a case control study in Northern Ethiopia.* BMC Infect Dis, 2013. **13**: p. 233.

142. Nakimuli-Mpungu, E., et al., *Psychological distress and adherence to highly active anti-retroviral therapy (HAART) in Uganda: a pilot study.* Afr Health Sci, 2009. **9 Suppl 1**: p. S2-7.

143. Nakimuli-Mpungu, E., et al., *Lifetime depressive disorders and adherence to anti-retroviral therapy in HIV-infected Ugandan adults: a case-control study.* J Affect Disord, 2013. **145**(2): p. 221-6.

144. Ukwe, C.V., et al., *Self-reported adherence to HAART in South-Eastern Nigeria is related to patients' use of pill box.* SAHARA J, 2010. **7**(1): p. 10-5.

145. Musumari, P.M., et al., *Food insecurity is associated with increased risk of non-adherence to antiretroviral therapy among HIV-infected adults in the Democratic Republic of Congo: a cross-sectional study.* PLoS One, 2014. **9**(1): p. e85327.

146. Etienne, M., et al., *Indicators of adherence to antiretroviral therapy treatment among HIV/AIDS patients in 5 African countries.* J Int Assoc Physicians AIDS Care (Chic), 2010. **9**(2): p. 98-103.

147. Negash, T. and V. Ehlers, *Personal factors influencing patients' adherence to ART in Addis Ababa, Ethiopia.* J Assoc Nurses AIDS Care, 2013. **24**(6): p. 530-8.

148. Nel, A. and A. Kagee, *The relationship between depression, anxiety and medication adherence among patients receiving antiretroviral treatment in South Africa.* AIDS care, 2013. **25**(8): p. 948-55.

149. Peltzer, K., et al., *Antiretroviral treatment adherence among HIV patients in KwaZulu-Natal, South Africa.* BMC public health, 2010. **10**: p. 111.

150. Tadios, Y. and G. Davey, *Antiretroviral treatment adherence and its correlates in Addis Ababa, Ethiopia.* Ethiop Med J, 2006. **44**(3): p. 237-44.

151. Amberbir, A., et al., *Predictors of adherence to antiretroviral therapy among HIV-infected persons: a prospective study in Southwest Ethiopia.* BMC public health, 2008. **8**: p. 265.

152. Tiyou, A., et al., *Predictors of adherence to antiretroviral therapy among people living with HIV/AIDS in resource-limited setting of southwest ethiopia.* AIDS research and therapy, 2010. **7**: p. 39.

153. Ramadhani, H.O., et al., *Predictors of incomplete adherence, virologic failure, and antiviral drug resistance among HIV-infected adults receiving antiretroviral therapy in Tanzania.* Clin Infect Dis, 2007. **45**(11): p. 1492-8.

154. Dlamini, P.S., et al., *HIV stigma and missed medications in HIV-positive people in five African countries.* AIDS Patient Care STDS, 2009. **23**(5): p. 377-87.

155. Pop-Eleches, C., et al., *Mobile phone technologies improve adherence to antiretroviral treatment in a resource-limited setting: a randomized controlled trial of text message reminders.* AIDS, 2011. **25**(6): p. 825-34.

156. Lester, R.T., et al., *Effects of a mobile phone short message service on antiretroviral treatment adherence in Kenya (WelTel Kenya1): a randomised trial.* Lancet, 2010. **376**(9755): p. 1838-45.

157. Ford, N., et al., *Early adherence to antiretroviral medication as a predictor of long-term HIV virological suppression: five-year follow up of an observational cohort.* PLoS One, 2010. **5**(5): p. e10460.

158. Taiwo, B.O., et al., *Assessing the viorologic and adherence benefits of patient-selected HIV treatment partners in a resource-limited setting.* J Acquir Immune Defic Syndr, 2010. **54**(1): p. 85-92.

159. Coetzee, B. and A. Kagee, *The development of an inventory to assess the structural barriers to clinic attendance and pill-taking amongst users of antiretroviral therapy.* AIDS Behav, 2013. **17**(1): p. 319-28.

160. Moshabela, M., et al., *Does accessibility to antiretroviral care improve after down-referral of patients from hospitals to health centres in rural South Africa?* Afr J AIDS Res, 2011. **10**(4): p. 393-401.

161. Federal Democratic Republic of Ethiopia Population Census Commission, *Summary and statistical report of the 2007 population and housing census*. 2008: Addis Ababa, Ethiopia.

162. AIDS and STDs Control Team, *AIDS in Ethiopia*. 2000, Ethiopian Ministry of Health Diseases Prevention and Control Department: Addis Ababa, Ethiopia

163. Ethiopian Minsistry of Health HIV/AIDS Prevention and Control Office, *AIDS in Ethiopia*, in *Sixth report*. 2010, HAPCO: Addis Ababa, Ethiopia.

164. Lester FT, Ayehunie S, and Zewdie D, *Acquired immunodeficiency syndrome: Seven cases in an Addis Ababa hospital.* Ethiopian Medical Journal, 1988. **26**(3): p. 139-145.

165. UNAIDS/WHO Working Group on Global HIV/AIDS and STI surveillance, *UNAIDS/WHO epidimological fact sheets on HIV/AIDS and sexually transmitted infections, 2004 update*. 2004, UNAIDS: Geneva, Switzerland

166. UNAIDS, *Global report: UNAIDS report on the global AIDS epidemic*. 2010: Geneva, Switzerland.

167. Ethiopian Ministry of Health HIV/AIDS Prevention and Control Office (HAPCO), *Country progress report on the HIV response*. 2014, HAPCO: Addis Ababa, Ethiopia

168. Assefa, Y., et al., *Scaling up antiretroviral treatment and improving patient retention in care: lessons from Ethiopia, 2005-2013.* Global Health, 2014. **10**: p. 43.

169. WHO Ethiopia Country Office, *Ethiopia update sheet on HIV/AIDS programe*. 2014, WHO Ethiopia country office Addis Ababa, Ethiopia.

170. Mengistu, Z. and A. Chere, *Adherence to antiretroviral therapy and its associated factors among people living with HIV/AIDS in Addis Ababa, Ethiopia.* Ethiop Med J, 2012. **50**(4): p. 355-361.

171. Giday, A. and W. Shiferaw, *Factors affecting adherence of antiretroviral treatment among AIDS patients in an Ethiopian tertiary university teaching hospital.* Ethiop Med J, 2010. **48**(3): p. 187-94.

172. Beyene, K.A., et al., *Highly active antiretroviral therapy adherence and its determinants in selected hospitals from south and central Ethiopia.* Pharmacoepidemiol Drug safety, 2009. **18**(11): p. 1007-1015.

173. Kebede, A. and N.T. Wabe, *Medication adherence and its determinants among patients on concomitant tuberculosis and antiretroviral therapy in South west ethiopia.* N Am J Med Sci, 2012. **4**(2): p. 67-71.

174. Tessema, B., et al., *Magnitude and determinants of nonadherence and nonreadiness to highly active antiretroviral therapy among people living with HIV/AIDS in Northwest Ethiopia: a cross - sectional study.* AIDS research and therapy, 2010. **7**: p. 2.

175. Markos, E., A. Worku, and G. Davey, *Adherence to ART in PLWHA and Yirgalem Hospital, South Ethiopia.* Ethiopian Journal of Health Development, 2009. **22**(2): p. 174-179.

176. Tsega, B., B.A. Srikanth, and Z. Shewamene, *Determinants of non-adherence to antiretroviral therapy in adult hospitalized patients, Northwest Ethiopia.* Patient preference and adherence, 2015. **9**: p. 373-80.

177. Mitiku, H., T. Abdosh, and Z. Teklemariam, *Factors affecting adherence to antiretroviral treatment in harari national regional state, eastern ethiopia.* ISRN AIDS, 2013. **2013**: p. 960954.

178. Ketema, A.K. and Z. Shewangizaw Weret, *Assessment of adherence to highly active antiretroviral therapy and associated factors among people living with HIV at Debrebrihan Referral Hospital and Health Center, Northeast Ethiopia: a cross-sectional study.* HIV AIDS (Auckl), 2015. **7**: p. 75-81.

179. Gusdal, A.K., et al., *Peer counselors' role in supporting patients' adherence to ART in Ethiopia and Uganda.* AIDS care, 2011. **23**(6): p. 657-62.

180. Balcha, T.T., A. Jeppsson, and A. Bekele, *Barriers to antiretroviral treatment in ethiopia: a qualitative study.* J Int Assoc Physicians AIDS Care (Chic), 2011. **10**(2): p. 119-25.

181. Lifson, A.R., et al., *Barriers to retention in care as perceived by persons living with HIV in rural Ethiopia: focus group results and recommended strategies.* J Int Assoc Provid AIDS Care, 2013. **12**(1): p. 32-8.

182. Mann, C.J., *Observational research methods. Research design II: cohort, cross sectional, and case-control studies.* Emerg Med J, 2003. **20**(1): p. 54-60.

183. Ethiopian Ministry of Health HIV/AIDS Prevention and Control Office (HAPCO), *Country progress report on HIV/AIDS response*. 2012, HAPCO: Addis Ababa, Ethiopia

184. Reniers, G., et al., *Steep declines in population-level AIDS mortality following the introduction of antiretroviral therapy in Addis Ababa, Ethiopia.* AIDS, 2009. **23**(4): p. 511-8.

185. Rokas, K.E., et al., *Role of Raltegravir in HIV-1 Management.* Ann Pharmacother, 2012. **46**(4): p. 578-89.

186. Assefa, Y., et al., *Effectiveness and acceptability of delivery of antiretroviral treatment in health centres by health officers and nurses in Ethiopia.* J Health Serv Res Policy, 2012. **17**(1): p. 24-9.

187. Carr, A., et al., *A randomised, open-label comparison of three highly active antiretroviral therapy regimens including two nucleoside analogues and indinavir for previously untreated HIV-1 infection: the OzCombo1 study.* AIDS, 2000. **14**(9): p. 1171-80.

188. Ethiopian Ministry of Health HIV/AIDS Prevention and Control Office (HAPCO), *Multi-sectoral HIV/AIDS response monitoring & evaluation report*. 2011, HAPCO: Addis Ababa, Ethiopia

189. Wubshet, M., et al., *High loss to followup and early mortality create substantial reduction in patient retention at antiretroviral treatment program in North-West Ethiopia.* ISRN AIDS, 2012.

190. Spire, B., et al., *Adherence to highly active antiretroviral therapies (HAART) in HIV-infected patients: from a predictive to a dynamic approach.* Soc Sci Med, 2002. **54**(10): p. 1481-96.

191. Ingersoll, K.S. and J. Cohen, *The impact of medication regimen factors on adherence to chronic treatment: a review of literature.* J Behav Med, 2008. **31**(3): p. 213-24.

192. Wasti, S.P., et al., *Factors influencing adherence to antiretroviral treatment in Asian developing countries: a systematic review.* Trop Med Int Health, 2012. **17**(1): p. 71-81.

193. Merten, S., et al., *Patient-reported barriers and drivers of adherence to antiretrovirals in sub-Saharan Africa: a meta-ethnography.* Trop Med Int Health, 2010. **15 Suppl 1**: p. 16-33.

194. Mbuagbaw, L., et al., *The Cameroon Mobile Phone SMS (CAMPS) trial: a randomized trial of text messaging versus usual care for adherence to antiretroviral therapy.* PLoS One, 2012. **7**(12): p. e46909.

195. van der Kop, M.L., et al., *The effect of weekly short message service communication on patient retention in care in the first year after HIV diagnosis: study protocol for a randomised controlled trial (WelTel Retain).* BMJ Open, 2013. **3**(6).

196. Oyugi, J.H., et al., *Multiple validated measures of adherence indicate high levels of adherence to generic HIV antiretroviral therapy in a resource-limited setting.* J Acquir Immune Defic Syndr, 2004. **36**(5): p. 1100-2.

197. Sikka, R., F. Xia, and R.E. Aubert, *Estimating medication persistency using administrative claims data.* Am J Manag Care, 2005. **11**(7): p. 449-57.

198. McMahon, J.H., et al., *Pharmacy adherence measures to assess adherence to antiretroviral therapy: review of the literature and implications for treatment monitoring.* Clin Infect Dis, 2011. **52**(4): p. 493-506.

199. Gill, C.J., et al., *No room for complacency about adherence to antiretroviral therapy in sub-Saharan Africa.* AIDS, 2005. **19**(12): p. 1243-9.

200. Wright, K., et al., *Stigma scale revised: reliability and validity of a brief measure of stigma for HIV+ youth.* J Adolesc Health, 2007. **40**(1): p. 96-8.

201. Sarna, A., et al., *Short- and long-term efficacy of modified directly observed antiretroviral treatment in Mombasa, Kenya: a randomized trial.* J Acquir Immune Defic Syndr, 2008. **48**(5): p. 611-9.

202. Berger, B.E., C.E. Ferrans, and F.R. Lashley, *Measuring stigma in people with HIV: Psychometric assessment of the HIV stigma scale.* Res Nurs Health, 2001. **24**(6): p. 518-529.

203. Vowles, K.E. and M. Thompson, *The patient-provider relationship in chronic pain.* Curr Pain Headache Rep, 2012. **16**(2): p. 133-8.

204. Balfour, L., et al., *Development and psychometric validation of the HIV Treatment Knowledge Scale.* AIDS Care, 2007. **19**(9): p. 1141-8.

205. Horne, R., J. Weinman, and M. Hankins, *The beliefs about medicines questionnaire: the development and evaluation of a new method for assessing the cognitive representation of medication.* Psychol Health, 1999. **14**(1): p. 1-24.

206. Horne, R., et al., *Doubts about necessity and concerns about adverse effects: identifying the types of beliefs that are associated with non-adherence to HAART.* Int J STD AIDS, 2004. **15**(1): p. 38-44.

207. Bova, C., et al., *Measuring patient-provider trust in a primary care population: Refinement of the health care relationship trust scale.* Res Nurs Health, 2012. **35**(4): p. 397-408.

208. WHO, *Monitoring and reporting adverse events*. 2003, WHO: Geneva, Switzerland.

209. Naranjo, C.A., et al., *A method for estimating the probability of adverse drug reactions.* Clin Pharmacol Ther, 1981. **30**(2): p. 239-245.

210. Pirmohamed, M., et al., *Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients.* BMJ, 2004. **329**(7456): p. 15-19.

211. Schumock, G.T. and J.P. Thornton, *Focusing on the preventability of adverse drug reactions.* Hosp Pharm, 1992. **27**(6): p. 538.

212. Falagas, M.E., et al., *Socioeconomic status (SES) as a determinant of adherence to treatment in HIV infected patients: a systematic review of the literature.* Retrovirology, 2008. **5**: p. 13.

213. Lamb, M.R., et al., *Association of Adherence Support and Outreach Services with Total Attrition, Loss to Follow-Up, and Death among ART Patients in Sub-Saharan Africa.* PLoS One, 2012. **7**(6): p. e38443.

214. Haberer, J.E., et al., *Multiple measures reveal antiretroviral adherence successes and challenges in HIV-infected Ugandan children.* PloS one, 2012. **7**(5): p. e36737.

215. WHO. *HIV/AIDS Media centre fact sheets*. 2014; Available from: http://www.who.int/mediacentre/factsheets/fs360/en/.

216. Michaels, S.H., R. Clark, and P. Kissinger, *Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection.* N Engl J Med, 1998. **339**(6): p. 405-6.

217. Bangsberg, D.R., *Less than 95% adherence to nonnucleoside reverse-transcriptase inhibitor therapy can lead to viral suppression.* Clin Infect Dis, 2006. **43**(7): p. 939-41.

218. Nachega, J.B., et al., *Adherence to nonnucleoside reverse transcriptase inhibitor-based HIV therapy and virologic outcomes.* Ann Intern Med, 2007. **146**(8): p. 564-73.

219. Nachega, J.B., et al., *Adherence to antiretroviral therapy during and after pregnancy in low-income, middle-income, and high-income countries: a systematic review and meta-analysis.* AIDS, 2012. **26**(16): p. 2039-52.

220. Delaugerre, C., et al., *Resistance profile and cross-resistance of HIV-1 among patients failing a non-nucleoside reverse transcriptase inhibitor-containing regimen.* J Med Virol, 2001. **65**(3): p. 445-8.

221. Parienti, J.J., et al., *Predictors of virologic failure and resistance in HIV-infected patients treated with nevirapine- or efavirenz-based antiretroviral therapy.* Clin Infect Dis, 2004. **38**(9): p. 1311-6.

222. Carrieri, P., et al., *The dynamic of adherence to highly active antiretroviral therapy: results from the French National APROCO cohort.* J Acquir Immune Defic Syndr, 2001. **28**(3): p. 232-9.

223. Ammassari, A., et al., *Correlates and predictors of adherence to highly active antiretroviral therapy: overview of published literature.* J Acquir Immune Defic Syndr, 2002. **31 Suppl 3**: p. S123-7.

224. Langebeek, N., et al., *Predictors and correlates of adherence to combination antiretroviral therapy (ART) for chronic HIV infection: a meta-analysis.* BMC Med, 2014. **12**: p. 142.

225. Bezabhe, W.M., et al., *Adherence to antiretroviral drug therapy in adult patients who are HIV-positive in Northwest Ethiopia: a study protocol.* BMJ Open, 2013. **3**(10): p. e003559.

226. Bova, C., et al., *The health care relationship (HCR) trust scale: development and psychometric evaluation.* Res Nurs Health, 2006. **29**(5): p. 477-88.

227. Justice, A.C., et al., *Development and validation of a self-completed HIV symptom index.* J Clin Epidemiol, 2001. **54 (Suppl 1)**: p. 77-90.

228. Radloff, L.S., *The CES-D scale a self-report depression scale for research in the general population.* Applied psychological measurement, 1977. **1**(3): p. 385-401.

229. Bush, K., et al., *The AUDIT alcohol consumption questions (AUDIT-C): an effective brief screening test for problem drinking. Ambulatory Care Quality Improvement Project (ACQUIP). Alcohol Use Disorders Identification Test.* Arch Intern Med, 1998. **158**(16): p. 1789-95.

230. Krizevski, R., et al., *Naturally occurring norephedrine oxazolidine derivatives in khat (Catha edulis).* Planta Med, 2012. **78**(8): p. 838-42.

231. Lazo, M., et al., *Patterns and predictors of changes in adherence to highly active antiretroviral therapy: longitudinal study of men and women.* Clin Infect Dis, 2007. **45**(10): p. 1377-85.

232. Kleinman, N.J., et al., *Antiretroviral therapy adherence measurement in non-clinical settings in South India.* AIDS Care, 2014. **27**(2): p. 248-254.

233. Singh, N., et al., *Adherence of human immunodeficiency virus-infected patients to antiretroviral therapy.* Clin Infect Dis, 1999. **29**(4): p. 824-30.

234. McMahon, J.H., et al., *Pharmacy and self-report adherence measures to predict virological outcomes for patients on free antiretroviral therapy in Tamil Nadu, India.* AIDS Behav, 2013. **17**(6): p. 2253-9.

235. Gonzalez, A., et al., *HIV symptom distress and anxiety sensitivity in relation to panic, social anxiety, and depression symptoms among HIV-positive adults.* AIDS Patient Care STDS, 2012. **26**(3): p. 156-64.

236. Reynolds, N.R., et al., *Factors influencing medication adherence beliefs and self-efficacy in persons naive to antiretroviral therapy: a multicenter, cross-sectional study.* AIDS Behav, 2004. **8**(2): p. 141-50.

237. Ironson, G., et al., *Distress, denial, and low adherence to behavioral interventions predict faster disease progression in gay men infected with human immunodeficiency virus.* Int J Behav Med, 1994. **1**(1): p. 90-105.

238. Gifford, A.L., et al., *Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens.* J Acquir Immune Defic Syndr, 2000. **23**(5): p. 386-95.

239. Remor, E., et al., *Perceived stress is associated with CD4+ cell decline in men and women living with HIV/AIDS in Spain.* AIDS care, 2007. **19**(2): p. 215-9.

240. Mugavero, M.J., et al., *Overload: impact of incident stressful events on antiretroviral medication adherence and virologic failure in a longitudinal, multisite human immunodeficiency virus cohort study.* Psychosom Med, 2009. **71**(9): p. 920-6.

241. Khalili, H., et al., *Antiretroviral induced adverse drug reactions in Iranian human immunodeficiency virus positive patients.* Pharmacoepidemiol Drug Saf, 2009. **18**(9): p. 848-57.

242. International Telecommunications Union, *Measuring the information society report: the ICT development index*. 2014, International Telecommunication Union: Geneva, Switzerland.

243. Liu, H., et al., *A comparison study of multiple measures of adherence to HIV protease inhibitors.* Ann Intern Med, 2001. **134**(10): p. 968-77.

244. Arnsten, J.H., et al., *Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring.* Clin Infect Dis, 2001. **33**(8): p. 1417-23.

245. White, B.L., et al., *Effect of directly observed antiretroviral therapy compared to self-administered antiretroviral therapy on adherence and virological outcomes among HIV-infected prisoners: a randomized controlled pilot study.* AIDS Behav, 2015. **19**(1): p. 128-36.

246. Shah, B., et al., *Adherence to antiretroviral therapy and virologic suppression among HIV-infected persons receiving care in private clinics in Mumbai, India.* Clin Infect Dis, 2007. **44**(9): p. 1235-44.

247. Press, N., et al., *Virologic and immunologic response, clinical progression, and highly active antiretroviral therapy adherence.* J Acquir Immune Defic Syndr, 2002. **31 Suppl 3**: p. S112-7.

248. Kahn, J.G., et al., *CD4 cell count and viral load monitoring in patients undergoing antiretroviral therapy in Uganda: cost effectiveness study.* BMJ, 2011. **343**: p. d6884.

249. WHO (2013) *Global update on HIV treatment 2013: Results, impacts and opportunities*

250. Ammassari, A., et al., *Self-reported symptoms and medication side effects influence adherence to highly active antiretroviral therapy in persons with HIV infection.* J Acquir Immune Defic Syndr, 2001. **28**(5): p. 445-9.

251. Cespedes, M.S. and J.A. Aberg, *Neuropsychiatric complications of antiretroviral therapy.* Drug Saf, 2006. **29**(10): p. 865-74.

252. Sagwa, E., et al., *Adverse events during treatment of drug-resistant tuberculosis: a comparison between patients with or without human immunodeficiency virus co-infection.* Drug Saf, 2013. **36**(11): p. 1087-96.

253. Abdissa, S.G., et al., *Adverse drug reactions associated with antiretroviral treatment among adult Ethiopian patients in a tertiary hospital.* Ethiop Med J, 2012. **50**(2): p. 107-13.

254. Tadesse, W.T., et al., *Self-reported adverse drug reactions and their influence on highly active antiretroviral therapy in HIV infected patients: a cross sectional study.* BMC Pharmacol Toxicol, 2014. **15**: p. 32.

255. Fowler, M.G. and M. Owor, *Monitoring HIV treatment in resource-limited settings: reassuring news on the usefulness of CD4(+) cell counts.* J Infect Dis, 2009. **199**(9): p. 1255-7.

256. Ethiopian Ministry of Health HIV/ AIDS Prevention and Control Office (HAPCO), *Guidelines for the managment of opportunistic infections and antiretroviral treatment in adolescents and adults in Ethiopia*. 2008.

257. WHO, *Antiretroviral therapy for HIV infection in adults and adolescents: recommendations for a public health approach 2010 revision*. 2010: Geneva, Switzerland

258. Edwards, I.R. and C. Biriell, *Harmonisation in pharmacovigilance.* Drug Saf, 1994. **10**(2): p. 93-102.

259. National Institute of Allergy and Infectious Diseases (December 2004, with clarification published on August 2009) *Division of AIDS table for grading the severity of adult and paediatric adverse events (DAIDS AE Grading Table)*.

260. Grabar, S., et al., *Clinical outcome of patients with HIV-1 infection according to immunologic and virologic response after 6 months of highly active antiretroviral therapy.* Ann Intern Med, 2000. **133**(6): p. 401-10.

261. Meresse, M., et al., *Patterns of adherence to antiretroviral therapy and HIV drug resistance over time in the Stratall ANRS 12110/ESTHER trial in Cameroon.* HIV Med, 2014. **15**(8): p. 478-87.

262. Sethi, A.K., et al., *Association between adherence to antiretroviral therapy and human immunodeficiency virus drug resistance.* Clin Infect Dis, 2003. **37**(8): p. 1112-8.

263. Shet, A., et al., *Influence of adverse drug reactions on treatment success: prospective cohort analysis of HIV-infected individuals initiating first-line antiretroviral therapy in India.* PLoS One, 2014. **9**(3): p. e91028.

264. Rudorf, D.C. and S.A. Krikorian, *Adverse effects associated with antiretroviral therapy and potential management strategies.* Journal of Pharmacy Practice, 2005. **18**(4): p. 258-277.

265. Reginald, O.O., et al., *Adverse reactions associated with antiretroviral regimens in adult patients of a university teaching Hospital HIV Program in Zaria, Northern Nigeria: An observational cohort study.* Journal of Antivirals & Antiretrovirals, 2012. **4**(1).

266. Cooper, C.L., et al., *Clinical outcomes of first antiretroviral regimen in HIV/hepatitis C virus co-infection.* HIV Med, 2006. **7**(1): p. 32-7.

267. Eluwa, G.I., T. Badru, and K.J. Akpoigbe, *Adverse drug reactions to antiretroviral therapy (ARVs): incidence, type and risk factors in Nigeria.* BMC Clin Pharmacol, 2012. **12**: p. 7.

268. Severe, P., et al., *Antiretroviral therapy in a thousand patients with AIDS in Haiti.* N Engl J Med, 2005. **353**(22): p. 2325-34.

269. Modayil, R.R., et al., *Adverse drug reactions to antiretroviral therapy (ART): an experience of spontaneous reporting and intensive monitoring from ART centre in India.* Pharmacoepidemiol Drug Saf, 2010. **19**(3): p. 247-55.

270. Bezabhe, W.M., et al., *Barriers and facilitators of adherence to antiretroviral drug therapy and retention in care among adult HIV-positive patients: a qualitative study from Ethiopia.* PLoS One, 2014. **9**(5): p. e97353.

271. Jena, A., et al., *Adverse drug reactions to nonnucleoside reverse transcriptase inhibitor-based antiretroviral regimen: a 24-week prospective study.* J Int Assoc Physicians AIDS Care (Chic), 2009. **8**(5): p. 318-22.

272. Nagpal, M., et al., *Adverse drug reactions to antiretroviral therapy in AIDS patients at a tertiary care hospital in India: A prospective observational study.* Indian J Med Sci, 2010. **64**(6): p. 245-52.

273. Kumarasamy, N., et al., *Spectrum of adverse events after generic HAART in southern Indian HIV-infected patients.* AIDS Patient Care STDS, 2008. **22**(4): p. 337-44.

274. Clark, R., *Sex differences in antiretroviral therapy-associated intolerance and adverse events.* Drug Saf, 2005. **28**(12): p. 1075-83.

275. Bersoff-Matcha, S.J., et al., *Sex differences in nevirapine rash.* Clin Infect Dis, 2001. **32**(1): p. 124-9.

276. Omer, H.M., et al., *Multiple drug intolerance syndrome: a large-scale retrospective study.* Drug Saf, 2014. **37**(12): p. 1037-45.

277. von Wyl, V., et al., *Adherence as a predictor of the development of class-specific resistance mutations: the Swiss HIV Cohort Study.* PloS one, 2013. **8**(10): p. e77691.

278. Simpson, K., et al., *Costs of adverse events among patients with HIV infection treated with nonnucleoside reverse transcriptase inhibitors.* HIV Med, 2014. **15**(8): p. 488-98.

279. Weiser, S.D., et al., *Food insecurity as a barrier to sustained antiretroviral therapy adherence in Uganda.* PloS one, 2010. **5**(4): p. e10340.

280. Fox, M.P., et al., *The impact of HIV/AIDS on labour productivity in Kenya.* Trop Med Int Health, 2004. **9**(3): p. 318-24.

281. Reisler, R.B., et al., *Grade 4 events are as important as AIDS events in the era of HAART.* J Acquir Immune Defic Syndr, 2003. **34**(4): p. 379-86.

282. Stone, V.E., et al., *Antiretroviral regimen complexity, self-reported adherence, and HIV patients' understanding of their regimens: survey of women in the her study.* J Acquir Immune Defic Syndr, 2001. **28**(2): p. 124-31.

283. Gurwitz, J.H., et al., *Incidence and preventability of adverse drug events in nursing homes.* Am J Med, 2000. **109**(2): p. 87-94.

284. Messou, E., et al., *Anthropometric and immunological success of antiretroviral therapy and prediction of virological success in west African adults.* Bull World Health Organ, 2008. **86**(6): p. 435-42.

285. Curioso, W.H., et al., *Understanding the facilitators and barriers of antiretroviral adherence in Peru: a qualitative study.* BMC Public Health, 2010. **10**: p. 13.

286. Patel, S., et al., *Perceptions regarding barriers and facilitators to combination antiretroviral therapy adherence among people living with HIV/AIDS in Gujarat, India: a qualitative study.* Indian J Sex Transm Dis, 2012. **33**(2): p. 107-11.

287. Portelli, M.S., et al., *Barriers to and facilitators of adherence to antiretroviral therapy among people living with HIV in Lao PDR: a qualitative study.* Asia Pac J Public Health, 2012. **27**(2): p. 778-788.

288. Palar, K., et al., *Livelihood experiences and adherence to HIV antiretroviral therapy among participants in a food assistance pilot in Bolivia: a qualitative study.* PLoS One, 2013. **8**(4): p. e61935.

289. Vyankandondera, J., et al., *Antiretroviral therapy drug adherence in Rwanda: perspectives from patients and healthcare workers using a mixed-methods approach.* AIDS care, 2013. **25**(12): p. 1504-12.

290. Assefa, Y., et al., *Outcomes of antiretroviral treatment program in Ethiopia: Retention of patients in care is a major challenge and varies across health facilities.* BMC Health Serv Res, 2011. **11**(1): p. 81.

291. Gusdal, A.K., et al., *Voices on adherence to ART in Ethiopia and Uganda: a matter of choice or simply not an option?* AIDS Care, 2009. **21**(11): p. 1381-7.

292. Amhara HIV/AIDS Prevention and Control Coordination Office (HAPCO). *HIV facts and figures-Amhara*. 2013; Available from: www.etharc.org/amhara/resources/.../amhara%20hivfacts.htm.

293. Ethiopian Central Statistical Agency, *Population 2011*. July 2012, Central Statistical Agency Addis Ababa, Ethiopia.

294. Corbin, J. and A. Strauss, *Grounded theory research: procedures, canons and evaluative criteria.* Zeitschrift Fur Soziologie, 1990. **19**(6): p. 418-427.

295. Wasti, S.P., et al., *Factors influencing adherence to antiretroviral treatment in Nepal: a mixed-methods study.* PLoS One, 2012. **7**(5): p. e35547.

296. Bygrave, H., et al., *Trends in loss to follow-up among migrant workers on antiretroviral therapy in a community cohort in Lesotho.* PLoS One, 2010. **5**(10): p. e13198.

297. Saether, S.T., et al., *Migrants' access to antiretroviral therapy in Thailand.* Trop Med Int Health, 2007. **12**(8): p. 999-1008.

298. Lima, V., et al., *Migration adversely affects antiretroviral adherence in a population-based cohort of HIV/AIDS patients.* Soc Sci Med, 2009. **68**(6): p. 1044-9.

299. Weiser, S., et al., *Barriers to antiretroviral adherence for patients living with HIV infection and AIDS in Botswana.* J Acquir Immune Defic Syndr, 2003. **34**(3): p. 281-8.

300. Coetzee, B., A. Kagee, and N. Vermeulen, *Structural barriers to adherence to antiretroviral therapy in a resource-constrained setting: the perspectives of health care providers.* AIDS Care, 2011. **23**(2): p. 146-51.

301. Weiser, S.D., et al., *Longitudinal assessment of associations between food insecurity, antiretroviral adherence and HIV treatment outcomes in rural Uganda.* AIDS, 2013. **28**(1): p. 115-120.

302. Musumari, P.M., et al., *"If I have nothing to eat, I get angry and push the pills bottle away from me": a qualitative study of patient determinants of adherence to antiretroviral therapy in the Democratic Republic of Congo.* AIDS Care, 2013. **25**(10): p. 1271-1277.

303. Kuschminder, K., L. Andersson, and M. Siegel, *Profiling Ethiopian migration: a comparison of characteristics of Ethiopian migrants to Africa, the middle east and the north*. 2012, Center of African Studies(CEA)/ISCTE-IUL, University Institute of Lisbon: Lisbon.

304. Gibson, M.A. and E. Gurmu, *Rural to urban migration is an unforeseen impact of development intervention in Ethiopia.* PLoS One, 2012. **7**(11): p. e48708.

305. Malcolm, A., et al., *HIV-related stigmatization and discrimination: Its forms and contexts.* Critical Public Health, 1998. **8**(4): p. 347-370.

306. Mutwa, P.R., et al., *Living situation affects adherence to combination antiretroviral therapy in HIV-infected adolescents in Rwanda: a qualitative study.* PLoS One, 2013. **8**(4): p. e60073.

307. Peltzer, K. and S. Ramlagan, *Perceived stigma among patients receiving antiretroviral therapy: a prospective study in KwaZulu-Natal, South Africa.* AIDS Care, 2011. **23**(1): p. 60-8.

308. Gonzalez, J.S., et al., *Physical symptoms, beliefs about medications, negative mood, and long-term HIV medication adherence.* Ann Behav Med, 2007. **34**(1): p. 46-55.

309. Adeneye, A.K., et al., *Limitations to access and use of antiretroviral therapy (ART) among HIV positive persons in Lagos, Nigeria.* World Health Popul, 2006. **8**(2): p. 46-56.

310. Stangl, A.L., et al., *A systematic review of interventions to reduce HIV-related stigma and discrimination from 2002 to 2013: how far have we come?* J Int AIDS Soc, 2013. **16**(3 Suppl 2): p. 18734.

311. Katz, I.T., et al., *Impact of HIV-related stigma on treatment adherence: systematic review and meta-synthesis.* J Int AIDS Soc, 2013. **16**(3 Suppl 2): p. 18640.

312. Brown, L., K. Macintyre, and L. Trujillo, *Interventions to reduce HIV/AIDS stigma: what have we learned?* AIDS Educ Prev, 2003. **15**(1): p. 49-69.

313. Yakasai, A.M., et al., *Once-daily antiretroviral therapy among treatment-experienced Muslim patients fasting for the month of Ramadan.* Trop Doct, 2011. **41**(4): p. 233-5.

314. Finocchario-Kessler, S., et al., *Baseline predictors of ninety percent or higher antiretroviral therapy adherence in a diverse urban sample: the role of patient autonomy and fatalistic religious beliefs.* AIDS Patient Care STDS, 2011. **25**(2): p. 103-11.

315. Wubshet, M., et al., *Death and seeking alternative therapy largely accounted for lost to follow-up of patients on ART in Northwest Ethiopia: a community tracking survey.* PLoS One, 2013. **8**(3): p. e59197.

316. Stutterheim, S.E., et al., *HIV status disclosure among HIV-positive African and Afro-Caribbean people in the Netherlands.* AIDS Care, 2011. **23**(2): p. 195-205.

317. Charurat, M., et al., *Patient retention and adherence to antiretrovirals in a large antiretroviral therapy program in Nigeria: a longitudinal analysis for risk factors.* PLoS One, 2010. **5**(5): p. e10584.

318. Aspeling, H.E. and N.C. van Wyk, *Factors associated with adherence to antiretroviral therapy for the treatment of HIV-infected women attending an urban care facility.* Int J Nurs Pract, 2008. **14**(1): p. 3-10.

319. Olupot-Olupot, P., et al., *Adherence to antiretroviral therapy among a conflict-affected population in Northeastern Uganda: a qualitative study.* AIDS, 2008. **22**(14): p. 1882-4.

320. Watt, M.H., et al., *"It's all the time in my mind": facilitators of adherence to antiretroviral therapy in a Tanzanian setting.* Soc Sci Med, 2009. **68**(10): p. 1793-800.

321. Murphy, D.A., et al., *Pilot trial of a disclosure intervention for HIV+ mothers: the tarck program.* J Consult Clin Psychol, 2011. **79**(2): p. 203-14.

322. Olley, B.O., *Improving well-being through psycho-education among voluntary counseling and testing seekers in Nigeria: a controlled outcome study.* AIDS Care, 2006. **18**(8): p. 1025-31.

323. Rotberg, R.I. and J.C. Aker, *Mobile phones: uplifting weak and failed states.* The Washington Quarterly, 2013. **36**(1): p. 111-125.

324. Rathavuth Hong, V.M., and Pav Govindasamy., *Factors associated with prevalent HIV infections among Ethiopian adults: Further analysis of the 2005 Ethiopia demographic and health survey.* 2008, Macro International Inc.: Calverton, Maryland, USA.

325. Palella, F.J., Jr., et al., *Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection. HIV Outpatient Study Investigators.* N Engl J Med, 1998. **338**(13): p. 853-60.

326. Bangsberg, D.R., et al., *Non-adherence to highly active antiretroviral therapy predicts progression to AIDS.* AIDS, 2001. **15**(9): p. 1181-3.

327. Kurth, A.E., et al., *Clinician practices and attitudes regarding early antiretroviral therapy in the United States.* J Acquir Immune Defic Syndr, 2012. **61**(5): p. e65-9.

328. Liberati, A., et al., *The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.* PLoS Med, 2009. **6**(7): p. e1000100.

329. UNDP, *Human development report*. 2014, UNDP: New York, USA.

330. DerSimonian, R. and N. Laird, *Meta-analysis in clinical trials.* Control Clin Trials, 1986. **7**(3): p. 177-88.

331. Hedges, L.V. and J.L. Vevea, *Fixed-and random-effects models in meta-analysis.* Psychological methods, 1998. **3**(4): p. 486-504.

332. Higgins, J.P., et al., *Measuring inconsistency in meta-analyses.* Bmj, 2003. **327**: p. 557-560.

333. Egger, M., et al., *Bias in meta-analysis detected by a simple, graphical test.* Bmj, 1997. **315**: p. 629-634.

334. Messou, E., et al., *Association between medication possession ratio, virologic failure and drug resistance in HIV-1-infected adults on antiretroviral therapy in Cote d'Ivoire.* J Acquir Immune Defic Syndr, 2011. **56**(4): p. 356-64.

335. Nellen, J.F., et al., *Which method of adherence measurement is most suitable for daily use to predict virological failure among immigrant and non-immigrant HIV-1 infected patients?* AIDS Care, 2009. **21**(7): p. 842-50.

336. San Lio, M.M., et al., *Evaluating adherence to highly active antiretroviral therapy with use of pill counts and viral load measurement in the drug resources enhancement against AIDS and malnutrition program in Mozambique.* Clin Infect Dis, 2008. **46**(10): p. 1609-1616.

337. Moore, D.M., et al., *Discordant immunologic and virologic responses to highly active antiretroviral therapy are associated with increased mortality and poor adherence to therapy.* J Acquir Immune Defic Syndr, 2005. **40**(3): p. 288-93.

338. Gross, R., et al., *A simple, dynamic measure of antiretroviral therapy adherence predicts failure to maintain HIV-1 suppression.* J Infect Dis, 2006. **194**(8): p. 1108-14.

339. McNabb, J., et al., *Adherence to highly active antiretroviral therapy predicts virologic outcome at an inner-city human immunodeficiency virus clinic.* Clin Infect Dis, 2001. **33**(5): p. 700-5.

340. Parienti, J.J., et al., *Average adherence to boosted protease inhibitor therapy, rather than the pattern of missed doses, as a predictor of HIV RNA replication.* Clin Infect Dis, 2010. **50**(8): p. 1192-7.

341. Bangsberg, D.R., et al., *Adherence to protease inhibitors, HIV-1 viral load, and development of drug resistance in an indigent population.* AIDS, 2000. **14**(4): p. 357-66.

342. Neogi, U., et al., *Long-term efficacy of first line antiretroviral therapy in Indian HIV-1 infected patients: a longitudinal cohort study.* PLoS One, 2013. **8**(1): p. e55421.

343. Li, J.Z., et al., *Relationship between minority nonnucleoside reverse transcriptase inhibitor resistance mutations, adherence, and the risk of virologic failure.* AIDS, 2012. **26**(2): p. 185-92.

344. Ekstrand, M.L., et al., *Suboptimal adherence associated with virological failure and resistance mutations to first-line highly active antiretroviral therapy (HAART) in Bangalore, India.* Int Health, 2011. **3**(1): p. 27-34.

345. Low-Beer, S., et al., *Adherence to triple therapy and viral load response.* J Acquir Immune Defic Syndr, 2000. **23**(4): p. 360-1.

346. Anude, C.J., et al., *Immuno-virologic outcomes and immuno-virologic discordance among adults alive and on anti-retroviral therapy at 12 months in Nigeria.* BMC Infect Dis, 2013. **13**: p. 113.

347. Biswas, B., et al., *Characterizing HIV medication adherence for virologic success among individuals living with HIV/AIDS: Experience with the CNS HIV Antiretroviral Therapy Effects Research (CHARTER) cohort.* J HIV AIDS Soc Serv, 2014. **13**(1): p. 8-25.

348. El-Khatib, Z., et al., *Adherence and virologic suppression during the first 24 weeks on antiretroviral therapy among women in Johannesburg, South Africa - a prospective cohort study.* BMC Public Health, 2011. **11**: p. 88.

349. Ti, L., et al., *Suboptimal plasma HIV-1 RNA suppression and adherence among sex workers who use illicit drugs in a Canadian setting: an observational cohort study.* Sex Transm Infect, 2014. **90**(5): p. 418-22.

350. Glass, T.R., et al., *Correlates of self-reported nonadherence to antiretroviral therapy in HIV-infected patients: the Swiss HIV Cohort Study.* J Acquir Immune Defic Syndr, 2006. **41**(3): p. 385-92.

351. Jordan, M.R., et al., *Correlates of HIV-1 viral suppression in a cohort of HIV-positive drug users receiving antiretroviral therapy in Hanoi, Vietnam.* Int J STD AIDS, 2009. **20**(6): p. 418-22.

352. Goldman, J.D., et al., *Simple adherence assessments to predict virologic failure among HIV-infected adults with discordant immunologic and clinical responses to antiretroviral therapy.* AIDS Res Hum Retroviruses, 2008. **24**(8): p. 1031-5.

353. Court, R., et al., *Short term adherence tool predicts failure on second line protease inhibitor-based antiretroviral therapy: an observational cohort study.* BMC Infect Dis, 2014. **14**: p. 664.

354. Carrieri, M.P., et al., *Impact of early versus late adherence to highly active antiretroviral therapy on immuno-virological response: a 3-year follow-up study.* Antivir Ther, 2003. **8**(6): p. 585-94.

355. Pasternak, A.O., et al., *Modest nonadherence to antiretroviral therapy promotes residual HIV-1 replication in the absence of virological rebound in plasma.* J Infect Dis, 2012. **206**(9): p. 1443-52.

356. Okonji, J.A., et al., *CD4, viral load response, and adherence among antiretroviral-naive breast-feeding women receiving triple antiretroviral prophylaxis for prevention of mother-to-child transmission of HIV in Kisumu, Kenya.* J Acquir Immune Defic Syndr, 2012. **61**(2): p. 249-57.

357. Cahn, P., et al., *Predictors of adherence and virologic outcome in HIV-infected patients treated with abacavir- or indinavir-based triple combination HAART also containing lamivudine/zidovudine.* Curr Med Res Opin, 2004. **20**(7): p. 1115-23.

358. Meresse, M., et al., *Time patterns of adherence and long-term virological response to non-nucleoside reverse transcriptase inhibitor regimens in the Stratall ANRS 12110/ESTHER trial in Cameroon.* Antivir Ther, 2013. **18**(1): p. 29-37.

359. Cohen, C.J., et al., *Week 96 efficacy and safety of rilpivirine in treatment-naive, HIV-1 patients in two Phase III randomized trials.* AIDS, 2013. **27**(6): p. 939-50.

360. Haubrich, R.H., et al., *The value of patient-reported adherence to antiretroviral therapy in predicting virologic and immunologic response. California Collaborative Treatment Group.* AIDS, 1999. **13**(9): p. 1099-107.

361. Muyingo, S.K., et al., *Patterns of individual and population-level adherence to antiretroviral therapy and risk factors for poor adherence in the first year of the DART trial in Uganda and Zimbabwe.* J Acquir Immune Defic Syndr, 2008. **48**(4): p. 468-75.

362. Nelson, M., et al., *Suboptimal adherence to darunavir/ritonavir has minimal effect on efficacy compared with lopinavir/ritonavir in treatment-naive, HIV-infected patients: 96 week ARTEMIS data.* J Antimicrob Chemother, 2010. **65**(7): p. 1505-9.

363. Shet, A., et al., *Effect of mobile telephone reminders on treatment outcome in HIV: evidence from a randomised controlled trial in India.* BMJ, 2014. **349**: p. g5978.

364. Tuldra, A., et al., *Prospective randomized two-Arm controlled study to determine the efficacy of a specific intervention to improve long-term adherence to highly active antiretroviral therapy.* J Acquir Immune Defic Syndr, 2000. **25**(3): p. 221-8.

365. Murphy, R.A., et al., *Second-line antiretroviral therapy: long-term outcomes in South Africa.* J Acquir Immune Defic Syndr, 2012. **61**(2): p. 158-63.

366. Nolan, S., et al., *Adherence and plasma HIV RNA response to antiretroviral therapy among HIV-seropositive injection drug users in a Canadian setting.* AIDS Care, 2011. **23**(8): p. 980-7.

367. El-Khatib, Z., et al., *Adherence to drug-refill is a useful early warning indicator of virologic and immunologic failure among HIV patients on first-line ART in South Africa.* PLoS One, 2011. **6**(3): p. e17518.

368. Lima, V.D., et al., *Risk of viral failure declines with duration of suppression on highly active antiretroviral therapy irrespective of adherence level.* J Acquir Immune Defic Syndr, 2010. **55**(4): p. 460-5.

369. Kitahata, M.M., et al., *Pharmacy-based assessment of adherence to HAART predicts virologic and immunologic treatment response and clinical progression to AIDS and death.* Int J STD AIDS, 2004. **15**(12): p. 803-10.

370. Abah, I.O., et al., *Clinical Utility of Pharmacy-Based Adherence Measurement in Predicting Virologic Outcomes in an Adult HIV-Infected Cohort in Jos, North Central Nigeria.* J Int Assoc Provid AIDS Care, 2014.

371. Simoni, J.M., et al., *Antiretroviral adherence interventions: a review of current literature and ongoing studies.* Top HIV Med, 2003. **11**(6): p. 185-98.

372. Kahana, S.Y., et al., *A meta-analysis of adherence to antiretroviral therapy and virologic responses in HIV-infected children, adolescents, and young adults.* AIDS Behav, 2013. **17**(1): p. 41-60.

373. Rosenblum, M., et al., *The risk of virologic failure decreases with duration of HIV suppression, at greater than 50% adherence to antiretroviral therapy.* PLoS One, 2009. **4**(9): p. e7196.

374. Viswanathan, S., et al., *Adherence and HIV RNA Suppression in the Current Era of Highly Active Antiretroviral Therapy.* J Acquir Immune Defic Syndr, 2015. **69**(4): p. 493-8.

375. Gupta, R.K., et al., *Global trends in antiretroviral resistance in treatment-naive individuals with HIV after rollout of antiretroviral treatment in resource-limited settings: a global collaborative study and meta-regression analysis.* Lancet, 2012. **380**(9849): p. 1250-8.

376. Haas, A.D., et al., *Monitoring and Switching of First-line Antiretroviral Therapy in sub-Saharan Africa: Collaborative Analysis of Adult Treatment Cohorts.* Lancet HIV, 2015. **2**(7): p. e271-e278.

377. Ioannidis, J.P., et al., *Comparison of evidence of treatment effects in randomized and nonrandomized studies.* JAMA, 2001. **286**(7): p. 821-830.

378. Glesby, M.J. and D.R. Hoover, *Survivor treatment selection bias in observational studies: examples from the AIDS literature.* Ann Intern Med, 1996. **124**(11): p. 999-1005.

379. Nieuwkerk, P.T. and F.J. Oort, *Self-reported adherence to antiretroviral therapy for HIV-1 infection and virologic treatment response: a meta-analysis.* J Acquir Immune Defic Syndr, 2005. **38**(4): p. 445-8.

380. Gardner, E.M., et al., *Durability of Adherence to Antiretroviral Therapy on Initial and Subsequent Regimens.* AIDS Patient Care STDS, 2006. **20**(9): p. 628-36.

381. Smith, H.J., J. Chen, and X. Liu, *Language and rigour in qualitative research: problems and principles in analyzing data collected in Mandarin.* BMC Med Res Methodol, 2008. **8**: p. 44.

382. Rachlis, B.S., E.J. Mills, and D.C. Cole, *Livelihood security and adherence to antiretroviral therapy in low and middle income settings: a systematic review.* PLoS One, 2011. **6**(5): p. e18948.

383. Sweeney, S.M. and P.A. Vanable, *The Association of HIV-Related Stigma to HIV Medication Adherence: A Systematic Review and Synthesis of the Literature.* AIDS Behav, 2016. **20**(1): p. 29-50.

384. Ampadu, H.H., et al., *Adverse Drug Reaction Reporting in Africa and a Comparison of Individual Case Safety Report Characteristics Between Africa and the Rest of the World: Analyses of Spontaneous Reports in VigiBase.* Drug Saf, 2016. **39**(4): p. 335-345.

385. Al-Dakkak, I., et al., *The impact of specific HIV treatment-related adverse events on adherence to antiretroviral therapy: a systematic review and meta-analysis.* AIDS care, 2013. **25**(4): p. 400-14.

386. Bisson, G.P., et al., *Pharmacy refill adherence compared with CD4 count changes for monitoring HIV-infected adults on antiretroviral therapy.* PLoS Med, 2008. **5**(5): p. e109.

Appendices

Appendix A. Prospective data collection tools Appendix

A.1. Baseline questionnaire

The information should be collected from ART clinic intake form (Patient registration form 1-6, Social assessment form 6-8). (Question number 2 should be filled by referring patients' medical record)

1. Do you have a completed consent form for this subject? ☐ No ☐ yes

2. Does this subject have any allergies? ☐ No ☐ yes
   Write a short description about the drug/s and reaction/s.

3. Age _____ (years)

4. Gender ☐ Female ☐ Male

5. Marital status:
   - ☐ Never Married
   - ☐ Married
   - ☐ Separated
   - ☐ Divorced
   - ☐ Widow/Widower

6. Level of education:
   - ☐ No education
   - ☐ Primary
   - ☐ Secondary
   - ☐ Tertiary

7. Religion:
   - ☐ Orthodox
   - ☐ Muslim
   - ☐ Protestant
   - ☐ Catholic
   - ☐ Other

8. Number of children living with patient _____

9. Employment:
   - ☐ Working full time
   - ☐ Working Part-time
   - ☐ Not working/studying due to ill health
   - ☐ Unemployed

10. Does anyone know about your HIV status:
    Family: ☐ Spouse ☐ offspring ☐ Parent/s ☐ siblings
    Others: ☐ Relative ☐ Friends

Appendix A.2. Socio-demographic questionnaire

1. **Date** ----------

2. How Administered? ☐ Self ☐ Interviewer ☐ Both

I. Instructions: please answer the following questions by placing a cross in the box around the appropriate response or writing your response in the given black space

1. How many meals do you afford to take in a day? 1 ☐ 2 ☐ 3 ☐ 4 ☐
2. How much is your monthly income in Ethiopian birr? ----------
3. How much do you pay for one -way transportation to collect antiretroviral drugs? -------
4. How much time in minutes it takes from your home to the hospital (one-way)? ----------
5. How much time in minutes on average do you wait in the hospital to collect antiretroviral drugs-----
6. Do you have your own mobile Phone? ☐ Yes ☐ No
7. If yes, do you use SMS function of your mobile? Yes ☐ No ☐

Appendix A.3. Substance abuse

People have various health habits. The following questions ask about your alcohol and khat use, past and current.

	Daily	Nearly every day	3 or 4 times a week	Once or twice a week	2 or 3 times a month	Once a month	Never
1. **How often have you had a drink containing alcohol – a glass of beer, wine, a mixed drink, or any kind of alcoholic beverage – in the last 30 days? Check one.** *If Never, skip ahead to question #4.*	6	5	4	3	2	1	0

	1 or 2 drinks per day(	3 or 4 drinks per day	5 or 6 drinks per day	7 or 8 drinks per day	9-11 drinks per day	12 or more drinks per day
2. **On days when you drank any alcoholic beverages in the last 30 days, how many drinks did you usually have altogether? By a drink we mean a can or glass of beer, a 4-ounce glass of wine, a 1-1/2 ounce shot of liquor, or a mixed drink with a 1-1/2 ounces of liquor?**	0	1	2	3	4	5

	Daily	Nearly every day	3 or 4 times a week	Once or twice a week	2 or 3 times a	Once a month	Never
3. **During the past 30 days, how often have you had 5 or more drinks of alcohol in a row, that is, within a couple of hours (e.g. 2-4 hours)? Check one.**	6	5	4	3	2	1	0

4. **Have you used khat within the past 6 months?** 1 **Yes** 2 **No**

	Daily	Nearly every day	3 or 4 times a week	Once or twice a week	2 or 3 times a month	Once a month
5. **If yes, how often do you chew khat currently?**	5	4	3	2	1	0

Appendix. A.4. Self-report adherence questionnaire

Instructions:

The answers you give on this form will be used to plan ways to help other people who must take pills on a difficult schedule. Please do the best you can to answer all the questions. If you do not wish to answer a question, please draw a line through it. If you do not know how to answer a question, ask your study nurse to help. Thank you for helping in this important study.

Questions 1 to 4 ask about your HIV medications that you took over the last seven days

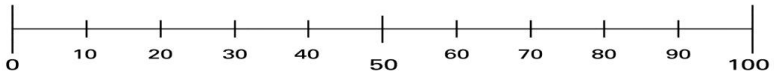
1. **Many patients find it difficult to make their HIV medications exactly as prescribed. If you took only a portion of a dose on any day(s) of the week, please report the dose(s) as being missed. How many dose(s) of your medication did you miss in the last 7 days?** --------

	Never	Some of the time	About half of the	Most of the time	All of the time
2. **Most anti-HIV medications need to be taken on schedule, such as 1 time a day or 2 times a day. How closely did you follow your specific schedule over the last 7 days?**	☐	☐	☐	☐	☐

3. **Do any of your anti-HIV medications have special instructions, such as "take with food" or "on an empty stomach" or "with plenty of fluids?** ☐ **ye** ☐ **No**

	Never	Some of the time	About half of	Most of the time	All of the time
4. **If yes, how often did you follow those special instructions over the last 7 days?**	☐	☐	☐	☐	☐

5. **Put a mark on line below at the point that shows best guess about how much of your prescribed HIV medication you have taken in the last month. We would be surprised if this were 100% for most people.**
   Examples:
   0% means you have taken no medication
   50% means you have taken half your medication
   100% means you have taken every single dose of your medication.



If you skip medications please answer the next set of questions under question number 6.

6. People may miss taking their medications for various reasons. Here is a list of possible reasons why you may miss taking your medications. How often have you missed taking your medications because you: (Tick one response for each question.)

	Never	Rarely	Some times	Often
1. Were away from home?	☐	☐	☐	☐
2. Were busy with other things?	☐	☐	☐	☐
3. Simply forgot?	☐	☐	☐	☐
4. Had too many pills to take?	☐	☐	☐	☐
5. Wanted to avoid side effects?	☐	☐	☐	☐
6. Did not want others to notice you taking medication?	☐	☐	☐	☐
7. Had a change in daily routine?	☐	☐	☐	☐
8. Felt like the drug was toxic/harmful?	☐	☐	☐	☐
9. Fell asleep/slept through dose time?	☐	☐	☐	☐
10. Felt sick or ill?	☐	☐	☐	☐
11. Felt depressed/overwhelmed?	☐	☐	☐	☐
12. Had problems taking pills at specified times (with meals, on empty stomach, fasting, etc.)?	☐	☐	☐	☐
13. Ran out of pills?	☐	☐	☐	☐
14. Felt good?	☐	☐	☐	☐
15. Were on traditional medicine?	☐	☐	☐	☐
16. Were on religious treatment such as holy water?	☐	☐	☐	☐

Appendix A.5. Social-support questionnaire

The following questions ask about your social support. Please place cross(x) in box crossponding to your response for each question.

	Very Dissatisfied	**Somewhat Dissatisfied**	**Somewhat satisfied**	**Very satisfied**	
1. In general, how satisfied are you with the overall support you get from your friends and family members?	☐	☐	☐	☐	
	Not at all	**A little**	**somewhat**	**A lot**	**Not appli cable**
2. To what extent do your friends or family members help you remember to take your medication?	☐	☐	☐	☐	☐
3. Did you use memory aid to take medications?	**Yes** ☐	**No** ☐			

Appendix A.6. HIV treatment knowledge scale

Please give one response for each question.

	False	True
1. Once the HIV viral load results are 'undetectable', HIV medications should be stopped.		
2. If HIV medications are not taken at the right time of day, HIV drug resistance can occur.		
3. HIV is cured when the HIV viral load blood test result is 'undetectable.		
4. Condoms during sex are not needed when the HIV viral load blood test results are at 'undetectable' levels		
5. It is better to take a half dose of HIV medications than to stop the HIV combination medications completely.		
6. One can get infected with a drug resistant type of HIV.		
7. HIV medications can cause unpleasant side effects (e.g. nausea, diarrhoea, vomiting).		
8. If sexual partners are both HIV-positive condoms are no longer needed.		
9. Treatments are available to reduce HIV medication side effects.		
10. Recreational drugs (e.g. ecstasy) can affect the effectiveness of HIV medications.		
11. Providing HIV medications to a pregnant woman reduces the baby's risk of being infected with HIV.		
12. There currently exists an HIV vaccine that prevents HIV infection.		
13. HIV medications can be taken at a different time of day on weekends or holidays.		
14. Over-the-counter herbal pills (e.g. St. John's Wort) could make HIV medications less effective.		
15. It is best to stop HIV medications as soon as you feel better.		
16. Missing a few doses of HIV pills can increase the amount of HIV virus in the body.		
17. After a few months, it becomes less important to take HIV medications at the right time of day.		
18. HIV medications help the body's immune system get stronger (CD4 increase).		
19. When HIV medications work well, the HIV viral load increases.		
20. Taking antibiotic medication protects a person from getting infected with HIV.		
21. Physical exercise (e.g. yoga, tai chi) can help reduce stress levels in HIV patients.		

Appendix A.7. HIV Symptom Index questionnaire

The following questions ask about symptoms you might have had during the past four weeks. Please check the box that describes how much you have been bothered by each symptom.

	I do not have this symptom	I have this symptom and …			
		It doesn't bother me	It bothers me a little	It bothers me a lot	It bothers me terribly
1. Fatigue or loss of energy?	☐	☐	☐	☐	☐
2. Fevers, chills or sweats?	☐	☐	☐	☐	☐
3. Feeling dizzy or lightheaded?	☐	☐	☐	☐	☐
4. Pain, numbness or tingling in the hands or feet?	☐	☐	☐	☐	☐
5. Trouble remembering?	☐	☐	☐	☐	☐
6. Nausea or vomiting?	☐	☐	☐	☐	☐
7. Diarrhea or loose bowel movements?	☐	☐	☐	☐	☐
8. Felt sad, down or depressed?	☐	☐	☐	☐	☐
9. Felt nervous or anxious	☐	☐	☐	☐	☐
10. Difficulty falling or staying asleep?	☐	☐	☐	☐	☐
11. Skin problems, such as rash, dryness or itching?	☐	☐	☐	☐	☐
12. Cough or trouble catching your breath?	☐	☐	☐	☐	☐
13. Headache?	☐	☐	☐	☐	☐
14. Loss of appetite or a change in the taste of food?	☐	☐	☐	☐	☐
15. Bloating, pain or gas in your stomach?	☐	☐	☐	☐	☐
16. Muscle aches or joint pain?	☐	☐	☐	☐	☐
17. Problems with having sex, such as loss of interest or lack of satisfaction?	☐	☐	☐	☐	☐
18. Changes in the way your body looks, such as fat deposits or weight gain?	☐	☐	☐	☐	☐
19. Problems with weight loss or wasting?	☐	☐	☐	☐	☐
20. Hair loss or changes in the way your hair looks?	☐	☐	☐	☐	☐

Appendix A. 8. Health care relationship scale

Directions: Listed below are 13 statements about patient and health care provider trust. Read each statement and decide which response best describes how you feel about your health care provider (the doctor, nurse practitioner, physician assistant or other primary care provider that manages the majority of your health care). Place an [X] in the box that corresponds with your response.

	None of the time	Some or a little of the time	Occasionally or a moderate amount of the	Most of the time	All of the time
1. How often does your health care provider discuss options and choices with you before health care decisions are made?					
2. My health care provider is committed to providing the best care possible.					
3. My health care provider is sincerely interested in me as a person.					
4. My health care provider is an excellent listener.					
5. My health care provider accepts me for who I am.					
6. My health care provider tells me the complete truth about my health-related problems.					
7. My health care provider treats me as an individual.					
8. My health care provider makes me feel that I am worthy of his/her time and effort.					
9. My health care provider takes the time to listen to me during each appointment.					
10. I feel comfortable talking to my health care provider about my personal issues.					
11. I feel better after seeing my health care provider.					
12. How often do you think about changing to a new health care provider?					
13. How often does your health care provider consider your need for privacy?					

Appendix A. 9. Centre for Epidemiological studies-depression scale (CES-D)

In the past week how often did you:(please circle one response for each question)

	Never/rarely	sometimes	often	Mostly or Always
1. Feel like you couldn't shake off the blues even with help from your family or friends?	☐	☐	☐	☐
2. Have trouble keeping your mind on what you were doing?	☐	☐	☐	☐
3. Feel that everything you did was an effort?	☐	☐	☐	☐
4. Have trouble sleeping?	☐	☐	☐	☐
5. Feel lonely?	☐	☐	☐	☐
6. Feel sad?	☐	☐	☐	☐
7. Feel like you just couldn't "get going"?	☐	☐	☐	☐

Appendix A.10. Berger-stigma scale

The following questions ask about your past experience. Please check one that fits your choice.

	Strongly disagree	disagree	agree	Strongly agree
1. I have been hurt by how people reacted to learning I have HIV	☐	☐	☐	☐
2. I have stopped socializing with some due to their reactions of my having HIV	☐	☐	☐	☐
3. I have lost friends by telling them I have HIV	☐	☐	☐	☐
4. I am very careful who I tell that I have HIV	☐	☐	☐	☐
5. I worry that people who know I have HIV will tell others	☐	☐	☐	☐
6. I feel that I am not as good a person as others because I have HIV	☐	☐	☐	☐
7. Having HIV makes me feel unclean.	☐	☐	☐	☐
8. Having HIV makes me feel that I'm a bad person.	☐	☐	☐	☐
9. Most people think that a person with HIV is disgusting.	☐	☐	☐	☐
10. Most people with HIV are rejected when others find out.	☐	☐	☐	☐

Appendix A. 11. Belief Medicine Questionnaire

We would like to ask you about your personal views about medicines prescribed for you. These are statements other people have made about their medicines. Please indicate the extent to which you agree or disagree with them by ticking the appropriate box. There are no right or wrong answers. We are interested in your personal views.

	Strongly disagree	Disagree	Uncertain	Agree	Strongly agree
1. My health, at present, depends on these medicines	☐	☐	☐	☐	☐
2. My life would be impossible without these medicines	☐	☐	☐	☐	☐
3. Without these medicines I would be very ill	☐	☐	☐	☐	☐
4. My health in the future will depend on these medicines	☐	☐	☐	☐	☐
5. These medicines keep my HIV under control	☐	☐	☐	☐	☐
6. Missing this medication for a day won' t matter in the long run	☐	☐	☐	☐	☐
7. These medicines are my best hope for the future	☐	☐	☐	☐	☐
8. These medicines keep me alive	☐	☐	☐	☐	☐
9. Having to take these medicines worries me	☐	☐	☐	☐	☐
10. I sometimes worry about long-term effects of these medicines	☐	☐	☐	☐	☐
11. These medicines are a mystery to me	☐	☐	☐	☐	☐
12. These medicines disrupt my life	☐	☐	☐	☐	☐
13. I sometimes worry about becoming too dependent on these medicines	☐	☐	☐	☐	☐
14. These medicines give me unpleasant side effects	☐	☐	☐	☐	☐
15. Using these medicines is embarrassing	☐	☐	☐	☐	☐
16. I am unlikely to get a bad side effect from this medication in the next month	☐	☐	☐	☐	☐
17. Taking this medication has been much worse than expected	☐	☐	☐	☐	☐
18. I have received enough information about anti HIV therapy	☐	☐	☐	☐	☐
19. The taste of this medication makes me feel unwell	☐	☐	☐	☐	☐

Appendix A.12.Medication record form

1010 UTAS
FACULTY OF HEALTH SCIENCE
School of Pharmacy

Medications

Record the medications.

Last edited by::

Drug Name	Type	DPD	IPD	Instructions	Date	QTY

If the drug regimen was changed from the previous supply, record the reason.

- Adverse drug reactions
- Pregnancy
- Failure of treatment
- Poor adherence
- Illness/hospitalisation
- Other …

Record any comments about this change.

Appendix A.13. Co-morbidity record form

1010 UTAS
FACULTY OF HEALTH SCIENCE
School of Pharmacy

Co-morbidites

Co-morbidity preamble

Last edited by:

Condition	AIDS related	Comments	Date Started	Date Ended

Appendix A.14. Laboratory record form

1010 UTAS
FACULTY OF HEALTH SCIENCE
School of Pharmacy

This form was last edited by: **Woldesellassie BEZABHE**

Test	Value	units
Date		
Weight		kg
Height		cm
CD4		Cells/mm3
Hepatits B		
Hepatits C		
Haemoglobin		g/dl
Haematocrit		%
WBC		Kcells/mm3
Absolute neutrophils		kcells/µL
Platelets		Kcells/mm3
Bilirubin Direct		mg/dl
Bilirubin Total		mg/dl
AST		IU/l
ALT		IU/l
ALP		IU/l
BUN		mg/dl
Serum creatinine		mg/dl
Urea		mmol/L
HIV AIDS stage		

Appendix A.15. Adverse drug report from

Adverse drug reactions

ADRS form preamble

Short description:

Date of onset:

Medications

Medication 1	Medication 2	Medication 3	Medication 4

Description

Severity	Causality	Preventable	Classification
• Grade 1 • Grade 2 • Grade 3 • Grade 4	• Definite • Probable • Possible • Doubtful	• No • Yes	• Toxicity • Side effect • Drug interaction • Immunological

Date resolution	Intervention	Intervention outcome	Outcome of ADR
	• Drug withdrawal • Symptomatic treatment • No Intervention	• Recovered • Continuing • Unknown	• Deceased • Not yet recovered • Recovered with sequlae

Hospital admissions	Length of stay

Appendix B. Prospective study patient Consent Form

UTAS FACULTY OF HEALTH SCIENCE School of Pharmacy

CONSENT FORM

Adherence with antiretroviral therapy in adult HIV-positive patients

1. I have read and understood the 'Information Sheet' for this project.
2. The nature and possible effects of the study have been explained to me.
3. I understand that the study involves me participating in a face to face, review of my medical record, and semi-structured interview at a time of my choosing relating to my experience of adverse drug reaction of antiretroviral drugs and adherence to the medication. This will occur during a normal appointment booked by the researcher.
4. I understand that participation involves no risk, However if I fill distressed during the discussion I will be free to either remove myself from the room or ask the facilitator to move the discussion in another direction.
5. I understand that all research data will be securely stored in the College of Medicine and Health Sciences at the Bahir-Dar University and in the School Of Pharmacy at the University of Tasmania premises for five years, and will then be destroyed [or will be destroyed when no longer required].
6. Any questions that I have asked have been answered to my satisfaction.
7. I agree that research data gathered from me for the study may be published provided that I cannot be identified as a participant.
8. I understand that the researchers will maintain my identity confidential and that any information I supply to the researcher(s) will be used only for the purposes of the research.
9. I agree to participate in this investigation and understand that I may withdraw at any time without any effect, and if I so wish may request that any data I have supplied to date be withdrawn from the research.

Name of Participant:

Signature:	Date:

Statement by Investigator

☐ The participant has received the Information Sheet where my details have been provided so participants have the opportunity to contact me prior to consenting to participate in this project.

Name of Investigator

Signature of Investigator

Name of investigator _____

Signature of investigator _____ Date _____

ADR and Adherence Consent Form [1] [1 October 2012]

Appendix C. Prospective study patient Information Sheet

UTAS FACULTY OF HEALTH SCIENCE School of Pharmacy

Tasmanian School of Pharmacy
Private Bag 26
HOBART TASMANIA 7001
Telephone (03) 6226 2190
Fax (03) 6226 7627

INFORMATION SHEET

Adherence with antiretroviral therapy in adult HIV-positive patients

All HIV/AIDS patients who are eligible for highly active antiretroviral therapy (HAART) are required to take their medicine for the rest of their life to suppress viral replication, improve their CD4 count, improve quality of live, and prolong survival. HAART is very effective in treatment of HIV/AIDS, but strict adherence to the regimen is required.

You are invited to participate in a research study which will assess adverse drug reactions, adherence and their predictors'. This study is being conducted in partial fulfillment of a PhD for Woldesellassie Bezabhe under the supervision of:

a. Prof. Gregory Peterson, Professor of Pharmacy, PhD, MBA
b. Dr. Luke Bereznicki, Senior Lecturer in Pharmacy Practice
c. Dr. Leanne Chalmers, Lecturer Pharmacy Practice

In addition Woldesellassie Bezabhe is a lecturer of Pharmacology, in College of Medicine and Health Sciences, Bahir-Dar University.

1. 'What is the purpose of this study?'

The introduction of HAART has made for HIV/AIDS chronic and manageable disease like other chronic diseases. This therapy improves quality of life and prolongs survival.

A number of patients are currently on HAART in Ethiopia. Adverse drug reactions from these drugs are very frequent in the first few months of the therapy. In addition, earlier strong adherence is recommended to combat the infection. However, the adherence rate and adverse effects in those patients who are naive to the therapy are not studied in Ethiopia.

The researchers wish to investigate adverse drug reactions, adherence rate and their determinate in treatment naïve patients, which will serve as an input for intervention study to improve adherence rate and adverse reactions management.

2. 'Why have I been invited to participate in this study?'

You are eligible to participate in this study because your Physician has decided for you to receive highly active antiretroviral therapy (HAART).

3. 'What does this study involve?'

The study involves you when you come to ART clinics for the first time to initiate antiretroviral drugs. You will be requested to participate in the study. If you are voluntary to participate in the study you will be invited to fill questionnaires with the assistance of pharmacists at the time of initiation of HAART. In addition you will be contacted every month for the first sixth months and every three month thereafter on your appointment date for one year and you will be interviewed about your experience of the treatment, especially adherence and ADRs of the drugs which will take about 20 to 30 minutes. Moreover, your medical record will also be accessed for documentation of your CD4 count, blood count, and ADRs.

It is important that you understand that your involvement in this study is voluntary. While we would be pleased to have you participate, we respect your right to decline. There will be no consequences to you if you decide not to participate, and this will not affect your treatment. If you decide to discontinue participation at any time, you may do so without providing an explanation. All information will be treated in a confidential manner, and your name will not be used in any publication arising out of the research. All of the research will be kept in a locked cabinet in the College of Medicine and Health Science at the Bahir-Dar University and School of Pharmacy at the University of Tasmania.

4. Are there any possible benefits from participation in this study?

Earlier strong adherence is recommended to combat the infection. In addition, adverse drug reactions from HAART are very frequent in the first few months of the therapy. However, in Ethiopia there is a scarcity of data regarding adverse reactions and adherence in patients who are naïve to HAART, especially at early stage of their therapy. This study will provide important information

regarding adherence and adverse effects and their predictors in those patients naïve to HAART and in the beginning of treatment. It will identify gaps in patients and health care system, pass the information to responsible bodies to manage adverse effect and improve adherence HIV/AIDS who will initiate HAART.

5. Are there any possible risks from participation in this study?

There are no specific risks anticipated with participation in this study.

6. What if I have questions about this research?

If you would like to discuss any aspect of this study please feel free to contact Dr. Mekdes Alemu (251) 920518328 or mekialemu@yahoo.com (Felege-Hiwot Hospital), Dr. Desalew Makonnen (251) 912013475 or desalewm@yahoo.com (Gondar University Hospital), who will be happy to discuss any aspect of the research with you. Once we have analyzed the information we will be mailing or emailing you a summary of our findings.

You are welcome to contact us at that time to discuss any issue relating to the research study.

This study has been approved by the Tasmanian Social Science Human Research Ethics Committee. If you have concerns or complaints about the conduct of this study should contact the Executive Officer of the HREC (Tasmania) Network on (03) 6226 7479 or email human.ethics@utas.edu.au. The Executive Officer is the person nominated to receive complaints from research participants. You will need to quote [*HREC project number*].

Thank you for taking the time to consider this study.
If you wish to take part in it, please sign the attached consent form.
This information sheet is for you to keep.

Appendix D. Prospective study Ethics approval letter

Office of Research Services
University of Tasmania
Private Bag 1
Hobart Tasmania 7001
Telephone + 61 3 6226 7479
Facsimile + 61 3 6226 7148
Email Human.Ethics@utas.edu.au
www.research.utas.edu.au/human_ethics/

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

31 October 2012

Professor Gregory Peterson
C/ School of Pharmacy

Sent via email

Dear Professor Peterson

REF NO: H0012722
TITLE: Adverse drug reactions and adherence with antiretroviral drug therapy in adult HIV-positive patients

PROTOCOL dated 23 Oct 2012
NEAF dated 23 Oct 2012
ACTG Adherence Baseline Questionnaire dated 26 Oct 2012
Information Sheet dated 23 Oct 2012
Consent Form
Adverse drug reaction Data collection sheet
Center for Epidemiological studies-Depression scale (CES-D)
Questionnaire Substance abuse
Health care relationship scale
HIV symptom Index (HIS)
HIV treatment Knowledge scale
Questionnaire Belief about medication (BMQ)
Questionnaire Berger-stigma scale
Questionnaire Social demographic: Social support: Self-reported adherence

The Tasmania Health and Medical Human Research Ethics Committee considered and approved the above documentation on **31 October 2012**.

This approval constitutes ethical clearance by the Health and Medical HREC. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approval of other bodies or authorities are required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

All committees operating under the Human Research Ethics Committee (Tasmania) Network are registered and required to comply with the *National Statement on the Ethical Conduct in Human Research* (NHMRC 2007 updated 2009).

Therefore, the Chief Investigator's responsibility is to ensure that:

(1) The individual researcher's protocol complies with the HREC approved protocol.

(2) Modifications to the protocol do not proceed until **approval** is obtained in writing from the HREC.

(3) Section 5.5.3 of the National Statement states:

Researchers have a significant responsibility in monitoring approved research as they are in the best position to observe any adverse events or unexpected outcomes. They should report such events or outcomes promptly to the relevant institution/s and ethical review body/ies and take prompt steps to deal with any unexpected risks.

The appropriate forms for reporting such events in relation to clinical and non-clinical trials and innovations can be located at the website below. All adverse events must be reported regardless of whether or not the event, in your opinion, is a direct effect of the therapeutic goods being tested.
http://www.research.utas.edu.au/human_ethics/medical_forms.htm

(4) All research participants must be provided with the current Patient Information Sheet and Consent Form, unless otherwise approved by the Committee.

(5) The Committee is notified if any investigators are added to, or cease involvement with, the project.

(6) This study has approval for 4 years contingent upon annual review. A *Progress Report* is to be provided on the anniversary date of your approval. Your first report is due 31 October 2013. You will be sent a courtesy reminder closer to this due date.

(7) A *Final Report* and a copy of the published material, either in full or abstract, must be provided at the end of the project.

Should you have any queries please do not hesitate to contact me on (03) 6226 2764.

Yours sincerely

Lauren Townsend
Ethics Administrator
Office of Research Services
Tel: +61 (0)3 6226 2764
Email: Lauren.Townsend@utas.edu.au
University of Tasmania, Private Bag 01 Hobart Tas 7001

ባህር ዳር ዩኒቨርሲቲ ጉምርና ማኅበረሰብ አገልግሎት ም/ፕሬዝዳንት ጽ/ቤት ባሕር ዳር - ኢትዮጵያ	 ከዓባይ ጓዳ ጥበብ ሲቀዳ Wisdom at the source of the Blue Nile	**Bahir Dar University** **Vice President for Research & Community Services** **Bahir Dar – Ethiopia**
✉ 79	☎ 251(0582) 20-01-43, 22 19 08 ፋክስ Fax - 251 (582) 20 20 25	**e-mail:infobdu@gmail.com** **website:www.bdu.edu.et**

ቁጥር
Ref. No. RCS/567/2004
ቀን
Date May 23, 2012

Applicant's name Mr. Woldesellassie M Bezabhe

Ethics Clearance Approval Form

Project Title:	Adverse drug reactions and adherence with antirretroviral drug therapy in adult HIV-Positive patients
Researchers Name (S)	Mr. Woldessellassie M Bezabhe
Principal Investigator	Mr. Woldessellassie M Bezabhe

Thank you for submitting your application for ethical clearance, which was considered at the Bahir Dar University's Ethics Committee **meeting on May 22, 2012**. The Committee has reviewed your Ethical Application, issues pertaining to participants, consent form, debriefing, and relevant questionnaires.

We are therefore pleased to inform you that the University's Ethics Clearance Committee (UECC) has approved your study from an ethical point of view.

Any serious adverse events or significant change which occurs in connection with this study and/or which may alter its ethical consideration must be reported immediately to us for a possible Ethical Amendment.

Yours sincerely,

Tésfaye Shiferaw Bogale (PhD)
Vice President for Research and Community Services

CC//
- Vice President for Academic Affairs
- Vice President for Research & Community Services
- Ethical Clearance Committee
- Research Senior Expert
  Bahir Dar University

Social Science Ethics Officer
Private Bag 01 Hobart
Tasmania 7001 Australia
Tel: (03) 6226 2763
Fax: (03) 6226 7148
Katherine.Shaw@utas.edu.au

HUMAN RESEARCH ETHICS COMMITTEE (TASMANIA) NETWORK

UTAS

14 January 2013

Professor Gregory Peterson
School of Pharmacy
Private Bag 26

Student Researcher: Woldesellassie Bezabhe

Sent via email

Dear Professor Peterson

Re: FULL ETHICS APPLICATION APPROVAL
Ethics Ref: **H0012845 - Barriers to, and facilitators of adherence to antiretroviral therapy among Ethiopian patients**

We are pleased to advise that the Tasmania Social Sciences Human Research Ethics Committee approved the above project on 13 January 2013.

This approval constitutes ethical clearance by the Tasmania Social Sciences Human Research Ethics Committee. The decision and authority to commence the associated research may be dependent on factors beyond the remit of the ethics review process. For example, your research may need ethics clearance from other organisations or review by your research governance coordinator or Head of Department. It is your responsibility to find out if the approval of other bodies or authorities is required. It is recommended that the proposed research should not commence until you have satisfied these requirements.

Please note that this approval is for four years and is conditional upon receipt of an annual Progress Report. Ethics approval for this project will lapse if a Progress Report is not submitted.

The following conditions apply to this approval. Failure to abide by these conditions may result in suspension or discontinuation of approval.

1. It is the responsibility of the Chief Investigator to ensure that all investigators are aware of the terms of approval, to ensure the project is conducted as approved by the Ethics Committee, and to notify the Committee if any investigators are added to, or cease involvement with, the project.

2. Complaints: If any complaints are received or ethical issues arise during the course of the project, investigators should advise the Executive Officer of the Ethics Committee on 03 6226 7479 or human.ethics@utas.edu.au.

3. Incidents or adverse effects: Investigators should notify the Ethics Committee immediately of any serious or unexpected adverse effects on participants or unforeseen events affecting the ethical acceptability of the project.

4. Amendments to Project: Modifications to the project must not proceed until approval is obtained from the Ethics Committee. Please submit an Amendment Form (available on our website) to notify the Ethics Committee of the proposed modifications.

5. Annual Report: Continued approval for this project is dependent on the submission of a Progress Report by the anniversary date of your approval. You will be sent a courtesy reminder closer to this date. **Failure to submit a Progress Report will mean that ethics approval for this project will lapse.**

6. Final Report: A Final Report and a copy of any published material arising from the project, either in full or abstract, must be provided at the end of the project.

Yours sincerely

Katherine Shaw
Ethics Officer
Tasmania Social Sciences HREC

Appendix E. Agreement between UTAS School of Pharmacy and Bahir-Dar University

School of Pharmacy

Bahir Dar University agreement form

EHIVE Project

Prospective study

Between EHIVE project, School of Pharmacy University of Tasmania Private Bag 26 Hobart TAS 7001 (The EHIVE project) Hobart Australia	And Bahir Dar University Research and Community Services Vice President Office P.O. Box 79 Fax 251-582202025 Bahir Dar Ethiopia

On behalf of Bahir Dar University, the Research and Community Services Vice President Office acknowledge that:

- All information contained in this document regarding the EHIVE project has been read and understood.
- The project is a follow-up study implemented in Felege-Hiwot and Gondar University Hospital.
- Assistant data collector will be employed in each hospital and will execute the following activities:
  - ✓ Approach interested participants and obtain consent from them.
  - ✓ Administering different questionnaires to participants based on the appointment date i.e. every month for the first six months and every 3 months thereafter.
  - ✓ Reviewing patients' medical records for collecting clinical and laboratory data.
  - ✓ Conducting pill count of patients' HIV-medication on the scheduled date.
  - ✓ Interviewing patients, carers and physicians to get more information on adverse drug reactions (ADR).
  - ✓ Data collectors will enter the data on EHIVE web database on daily basis and scan and attach the completed questionnaires on web database.
  - ✓ Perform assessment of the ADR data using validated algorithms.
  - ✓ Assist as note taker in the interview and focus group discussion of the qualitative study.
- Data collectors will ensure all data are collected as planned based on the participants' appointment dates.
- Data collectors will not disclose any information regarding the documentation system or any personal data collected to persons not involved with the EHIVE project.
- Data collectors employed in this project are required to complete individual agreement forms.
- Some nurses in the ART clinics of both hospitals will be involved in the recruitment of study participants.
- The University will take responsibility for engaging and reimbursing two physicians and a language expert to review the questionnaires.
- Patients will participate in an interview while nurses and peer counsellors working in the ART clinics will participate in the focus group discussion.
- Language experts will participate in translation, back translation, and panel discussion as a part of the qualitative study.
- Data clerks in each hospital will assist data collectors in finding patient medical records.
- Accountants assist in making balance and audit of the project money.
- All study participants agreeing to participate in this study are required to complete consent forms.

Funding: This project is funded by the Tasmanian School of Pharmacy, University of Tasmania.

The payment for each personnel involved in the research activity will be as described in the table below:

Milestone No.	Description	To be completed by: (These times are indicatives and might vary)	Amount (AUD)
1.	Employment of 2 data collector(s) at a rate of 370 AUD/month (equivalent to 6660 Birr/month) for a total of approx. 15 months from 01 Nov 2012 to 30 Jan 2014	November 2012 to January 2014	$11100
2.	Internet allowance for data collectors at 30 AUD/month (equivalent 540 Birr per month)	November 2012 to January 2014	$900
3.	Internet allowance for investigator at 35AUD/month (equivalent 630 Birr)	November 2012 to October 2013	$420
4.	Reimbursement of up to 4 nurses for patient recruitment activities at AUD60 each (equivalent to 1080)	November 2012 to January 2013	$240
5.	Engagement and payment of 2 physicians to review questionnaires at AUD50 each (equivalent to 900 Birr)	November 2012 to December 2012	$100
6.	Engagement and payment of 1 language expert review questionnaires at AUD100 (equivalent to 1800 Birr)	October 2012	$100
7.	Information evenings at each hospitals at AUD	November 2012	$200
8.	224 Participants reimbursement of transport and time spent at appointment date for each patient AUD3 (equivalent to 54 Birr)	November 2012 to January 2014	$5376
9.	Investigator per dim (b/n Australia and Ethiopia), for one way 350AUD (Equivalent 6300 Birr)	November 2012 to January 2014	$700
10.	Investigator per dim (Bahir Dar To Gondar) Per day 30 AUD per day (Equivalent 540 Birr per day)	November 2012 to January 2014	$1050
11.	One accountant making balance 4 times during the study period each payment AUD20 (equivalent to 360 Birr)	November 2012 to January 2014	$80
12.	Medical record Finders one person in each Hospital at AUD6 (equivalent 108 Birr) 5 times in the study period	November 2012 to January 2014	$60
13.	Two-way transport b/n Gondar and Bahir-Dar at AUD 18 (equivalent to 324 Birr)	November 2012 to January 2014	$144
14.	Laser Jet Scanner one for each site at AUD200 (equivalent 3600 Birr)	November 2012	$400
15.	Laser Jet printer one for each site at AUD300 (equivalent 5400 Birr)	November 2012	$600
16.	Consumable stationary items printing paper, photocopy and printer ink, gown, bag, CDMA apparatus...at AUD766 (equivalent 13788 Birr)	November 2012 to January 2014	$766
17.	28 Peer counsellor and Nurses reimbursement at AUD8 each (equivalent 150 Birr)	Feb 2013 to March 2013	$224
18.	25 Patient Participants in the qualitative	Feb 2013 to March	$150

Funding: This project is funded by the Tasmanian School of Pharmacy, University of Tasmania.

Milestone No.	Description	To be completed by: (These times are indicatives and might vary)	Amount (AUD)
	reimbursement payment at AUD6 each (equivalent 100 Birr)	2013	
19.	Interviewer per dim (Gondar interview) 20 days at AUD30 (equivalent to 540 Birr) per day	Feb 2013 to March 2013	$600
20.	Two translator for concept and categories in qualitative study at AUD150 each (equivalent 2700 Birr)	April 2013	$300
21.	4 panel discussion participant at AUD 50 per two days (equivalent 900 Birr)	April 2013	$200
22.	Soft drink, tea,...for about 50 participants at AUD 2 each (equivalent 36 Birr)	April 2013	$100
23.	Transport two way for 5 times at AUD 18 (equivalent 324 Birr)	Feb 2013 to March 2013	$90
24.	One Audio recorder AUD 50 (Equivalent 900 Birr)	Feb 2013	$50

The EHIVE project agrees to:

- Up on receipt of an invoice for the total amount, we will transfer **23,950 AUD** (equivalent to 431, 100 Ethiopian Birr) to Bahir Dar University for covering costs incurred in implementing the project as detailed above.
- Provide adequate training and technical support for data collectors.
- Maintain the confidentiality of all the data that is collected. All patients' specific information will be de-identified before analysis. Any publication that arises from this work will not include any information that will enable identification of individual patients, data collectors and others involved in the project. All data collected by data collectors will be transferred to the School of Pharmacy on a daily basis and will only be accessible to researchers for research purposes. All research data will be securely stored on the University of Tasmania premises and will be destroyed when no longer required.

Signed: _____ Date: 12/10/12

Name Tsefaye Shiferaw Logale (Ph.D)
Vice President for Research & Community Service
Research and community services
Vice presedent, Bahir-Dar University

Signed: _____ Date: 13/10/12

Gregory Peterson
Head, School of Pharmacy
University of Tasmania
Fax: 03-62267627 Phone:62261080

Funding: This project is funded by the Tasmanian School of Pharmacy, University of Tasmania.

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Wisdom at the source of the Blue Nile

Bahir Dar University
Vice President for Research & Community Services
Bahir Dar - Ethiopia

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☎ 251(582) 20-01-43, 22 19 08
ፋክስ Fax - 251 (582) 20 20 25
e-mail:infobdu@gmail.com
website:www.bdu.edu.et

ቁጥር Ref. No. 1 / 2883/2'6
ቀን Date 03-11-2012

To: School of Pharmacy
University of Tasmania
Hobart
Australia

Subject: Request for the transfer of EHIVE project money

Based on our previous agreement on EHIVE project "adherence with antiretroviral drug therapy in adult HIV-positive patients", I request your good office to transfer the EHIVE project money, 23,950 Australian Dollar (AUD), in the equivalent amount of Ethiopian Birr to the account given below.

Full name of the account holder: Bahir Dar University
Address of the account holder: Bahir Dar, Ethiopia
Account number: 703C21002883
Full bank name: Commercial Bank of Ethiopia
Full bank address: Bahir Dar, Ethiopia
Swift code: CBE TE TAA

With regards!

Tesfaye Shiferaw Bogale (Ph.D)
Vice President for Research & Community Service

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